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Bridging the gap between the genotype and the phenotype: linking genetic variation, selection and adaptation in fishes

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Abstract

One of the most challenging problems in evolutionary biology is linking the evolution of the phenotype with the underlying genotype, because most phenotypes are encoded by many genes that interact with each other and with the environment. Further, many phenotypes are correlated and selection on one can affect evolution of the other. This challenge is especially important in fishes, because their evolutionary response to harvest, global warming and conservation actions are among the least understood aspects of their management. Here, we discuss two major genetic approaches to studying the evolution of complex traits, multivariate quantitative genetics and molecular genetics, and examine the increasing interaction between the two fields. These interactions include using pedigree-based methods to study the evolution of multivariate traits in natural populations, comparing neutral and quantitative measures of population structure, and examining the contribution that the two approaches have made to each other. We then explore the major role that quantitative genetics is playing in two key issues in the conservation and management of fish populations: the evolutionary effects of fishing and adaptation to climate change. Throughout, we emphasize that it is important to anticipate the availability of improvements in molecular technology and statistical analyses by creating research populations such as inbred lines and families segregating at fitness traits, developing approaches to measuring the full range of phenotypes related to fitness, and collecting biological material and ecological data in natural populations. These steps will facilitate studies of the evolution of complex traits over informative temporal and spatial scales.

Keywords Climate change, fisheries-induced selection, genomics in fishes, multivariate quantitative genetics, phenotypic evolution

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Introduction

The remarkable advances of molecular genetics that have uncovered the staggering complexity of the genome have ushered in a new era in evolutionary biology. Geneticists can now characterize patterns of genetic variation across broad reaches of the genome for many taxa and catch glimpses of the ramifications of genetic variation for the whole organism. Nevertheless, one of the oldest problems in evolutionary biology – determining the relationships between the processes underlying genetic variation, the expression of the phenotype 1 and the consequences for fitness (Fig. 1) – remains largely unsolved a half century after the discovery of DNA (Barker and Thomas 1987; Stern 2000). This situation is especially challenging for biologists investigating adaptation to direct and indirect sources of human-induced selection.

In fish species, geneticists have been especially successful in determining population structure and gene flow, assigning individuals to source populations (Waples *et al.* 2008), determining mating structure and reproductive success, examining the effects of population size on genetic drift (Hauser and Carvalho 2008) and using gene expression as an indicator of physiological state (Goetz and MacKenzie 2008). However, some of the key challenges remaining in the conservation and management of fishes concern understanding and predicting adaptive responses in fish populations. Specifically, we need to be able to identify natural environmental influences on the evolution of the phenotype and then to anticipate how populations might respond to human activities such as fishing, global environmental change, habitat changes and conservation actions. There is growing recognition that these influences are important in shaping the evolution of fish populations – exemplified by the recent and high profile debate about the long-term effects of fishing (Jørgensen *et al.* 2007; Kuparinen and Merilä 2007) – but we do not understand quantitatively how populations will respond now or in the future. Upon achieving such an understanding, this knowledge will allow us to alter human activities to reduce their impacts on natural populations.

Many of the phenotypic characters that respond to evolution, such as growth rate, age and size at maturity, thermal tolerance and fecundity are

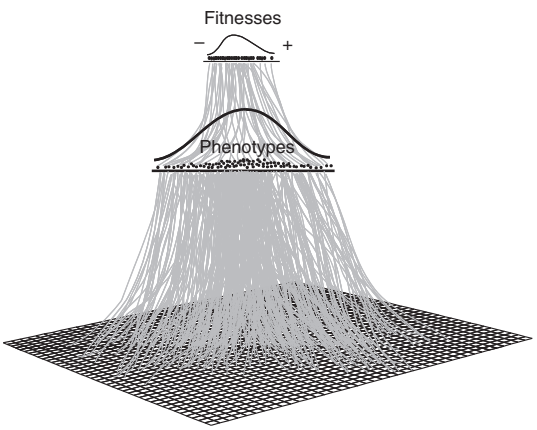

Figure 1 An idealized depiction of the general relationship between distributions of genotypes, phenotypes, and fitnesses in a population. The vast array of multilocus genotypes that occurs in a population are sampled at time of breeding to give rise, through development and under the influence of environmental variation, to a much smaller distribution of phenotypes (shown here as a simple univariate distribution). These phenotypes, in turn, have a smaller distribution of fitnesses (i.e., many phenotypes have similar fitness), again depending in part on stochastic factors. The relationships are not meant to reflect actual variation in scale or dimension—the distribution of phenotypes is multidimensional when more than one trait is considered. Relative fitnesses are arranged from lower (–) to higher (+).

complex and quantitative in nature. That is, they are coded by many interacting genes, which are in turn influenced in their expression by the environment. As an example, growth rate may be partly affected by genes encoding appetite, lipid storage and metabolism, but realized growth is also dependent on food availability. To further complicate matters, the evolution of a specific trait can also be affected by correlated traits; somatic growth may be impeded by maturation and in this case, growth rate will be negatively correlated with age at maturity. In most situations, we neither know the phenotypic effects of any particular gene nor can we reliably predict the consequences for fitness of those phenotypic changes. We rarely know to what extent specific mutations vary in their phenotypic effects or whether the distribution of allelic effects on the phenotype is broad or narrow. Given these limitations, how do we best use the tools we have at our disposal to improve our understanding of evolution, and to anticipate evolutionary response to natural and anthropogenic sources of selection? What can we expect to learn in the foreseeable future, especially for species as poorly understood as most fishes? Here, we attempt to address these questions by first identifying the conceptual and practical challenges associated with the study of quantitative traits, briefly outlining the available techniques for their study, and providing an overview of major contributions that have been made in the integration of statistical and DNA-based studies to date. We close by attempting to provide some insight into the current arguments and future development of the discipline within the context of the conservation and management of fishes.

Conceptual and practical challenges

Quantitative traits are typically polygenic, with most constituent loci unidentified and having an unknown distribution of alleles (Falconer and Mackay 1996). Besides being influenced by environmental variation, their expression might also be affected by non-additive genetic effects; factors that cannot be attributed to the simple substitution of an allele at a locus. These include dominance (one allele masks the phenotypic expression of another at the same locus), epistasis (interaction between alleles at different loci), pleiotropy (a single gene influences more than one phenotype) and linkage (inheritance of alleles at linked loci is not independent, because the alleles are physically located near each other on a chromosome arm). Most of these non-additive effects are assumed to be negligible in many analyses (Falconer and Mackay 1996). Most empirical work has focused on single traits at a time, but because of pleiotropy and because selection acts on multiple traits, trait expression is frequently correlated and the composite consequences of selection are often difficult to predict (Lynch and Walsh 1998; McGuigan 2006). Thus, selection response can be impeded or augmented by the genetic architecture of fitness-related traits. Within a population, the genetic architecture of trait expression is the foundation for understanding limits to phenotypic evolution in the short term, perhaps up to 25 generations. Spatial distribution of genetic variation among populations is important, because adaptation to a changing environment depends on this distribution.

We must be mindful of several complicating factors affecting interpretation of quantitative trait variation. Similarities in phenotypes may themselves mask differences in the underlying genetic architecture. As examples, the same phenotype might arise through selection on the same allele, or alternatively, through the expression of different genetic pathways (Arendt and Reznick 2008). A phenotype might appear constant across an environmental gradient, but this consistency masks evolution towards an optimal phenotype, a phenomenon known as counter-gradient evolution (Conover and Schultz 1995). In addition, different phenotypes may be produced by the same genotype in response to environmental cues (phenotypic plasticity; Stearns and Koella 1986; Roff 1997) in order to increase fitness when the environment is highly unpredictable. Phenotypic plasticity might be favoured over genetic polymorphism in variable environments when organisms can respond appropriately to environmental cues (Bradshaw 1986), and the degree of plasticity may itself be influenced genetically and evolve under selection (Pigliucci 2005). The amount of environmental unpredictability will have a large impact on to what degree the different adaptive mechanisms are employed (Orzack 1985; Bradshaw 1986), but long-term evolution and viability ultimately require sufficient genetic variability for these forms of adaptation to be expressed.

The most immediate problem in the practical study of quantitative traits is the separation of environmental and genetic influences on the phenotype. Rearing individuals together in the same

environment provides some clue to whether different phenotypes arise through genotypic differences, or if they are simply a result of environmental variation and are alternative expressions of the same genotypes. However, to fully understand the evolution of quantitative traits, it is necessary to provide a conceptual or mechanistic basis to their description. Until recently, statistical and molecular genetics have developed largely along independent paths within the discipline of quantitative genetics, but the future strength of the field lies in their integration. Here, we briefly describe innovations in these approaches that make this integration possible.

Innovations in characterizing quantitative traits

Multivariate quantitative genetics

Statistical genetic analysis of phenotypic variation provides an accessible and direct means of determining the direction and rate of evolutionary change (Lande 1976, 1979; Lande and Arnold 1983) and recent advances have permitted more realistic descriptions of the evolution of correlated traits. Response to selection requires phenotypic variation, genetic variation and differential reproduction or survival. With knowledge of a population's pattern of relatedness, and hence the inheritance of traits, the responses to selection can be predicted from trait variances, covariances and estimates of selection.

The framework for relating response to selection (R) to single trait variation and selection intensity relies on the empirical breeders' equation, $R = h^2S$ (Falconer and Mackay 1996). R represents the change in the population's phenotypic mean for the trait from generation to generation, h^2 is the trait narrow-sense heritability and S is the difference between the phenotypic mean of all potential breeders before selection, and those that survive selection (before they reproduce) within the same generation. The narrow-sense heritability, h^2, is a measure of the genetic variation of a trait within a population and is estimated by scaling the additive genetic variance V_A by the total phenotypic variation (measured by V_P, the phenotypic variance, so that $h^2 = V_A/V_P$). V_A in turn describes variation in the composite expression of the trait's constituent genes or the variance of individual breeding values within a population. Therefore, a large (or 'high') heritability value in a trait implies that most of the phenotypic variation is explained by genetic variation; it is not a measure of the proportion of the phenotype transmitted to the next generation, it does not assume that environmental variation is small and it is not an estimate of genetic determination (Visscher *et al.* 2008). Similarly, a small heritability is not necessarily because of a low V_A; rather, a small value means that genetic variation explains little of the phenotypic variation observed.

Because a comprehensive understanding of the evolutionary consequences of selection on several traits at once requires consideration of their genetic and phenotypic relationships, a multivariate form of the breeders' equation is required. For discrete generations, the equation is (Lande 1979; Lande and Arnold 1983):

$$\Delta \boldsymbol{z} = \boldsymbol{G}\boldsymbol{P}^{-1}\boldsymbol{s}$$

where $\Delta \boldsymbol{z}$ is the $(n \times 1)$ vector of changes across one or more generations in phenotypic means for the traits evaluated; $\boldsymbol{G}$ is the genetic covariance matrix composed of the additive genetic variances of, and covariances among the traits (an $n \times n$ matrix, Table 1); $\boldsymbol{P}^{-1}$ is the inverse of the phenotypic covariance matrix (an $n \times n$ matrix); and $\boldsymbol{s}$ is the vector of corresponding selection differentials (an $n \times 1$ vector). The matrix product $\boldsymbol{P}^{-1}\boldsymbol{s}$ is referred to as the multivariate selection gradient, often designated by the vector $\boldsymbol{\beta}$. Each element in $\boldsymbol{\beta}$ represents the gradient of the relative fitness surface for each trait, scaled by the trait's variance and its covariance with the other traits. Consideration of multiple traits that share genes provides a more accurate picture of potential response to selection, because it can capture the retardation or augmentation of selection response that results from genetic covariance among traits (McGuigan 2006). Therefore, $\boldsymbol{G}$ influences the rate and direction of evolution in traits that covary with the traits under direct selection.

An examination of the multivariate breeders' equation highlights several key points. First, although the $\boldsymbol{G}$ matrix is a statistical abstraction, it is based on well-tested genetic parameters: the additive variance and covariances (Cov_A) between traits. The matrix thus evolves through the same processes that result in allele frequency changes: namely, selection, drift, mutation and migration (Phillips and McGuigan 2006). Therefore, $\boldsymbol{G}$ can be used to identify differences among populations in their ability to evolve, and the multivariate equation

Table 1 Description of the structure of a ***G*** matrix. A. The additive genetic variances (in bold) underlying the traits lie along the diagonal of the symmetrical matrix; the values above and below the diagonal denote the additive genetic covariances between each pair of correlated traits. B. Example of a ***G*** matrix derived for Chinook salmon *Oncorhynchus tshawytscha* (Hard 2004; Hard JJ., unpublished data). Values were estimated with restricted maximum likelihood methods from a spawning population comprising full sibs and half sibs.

(A)

$\mathbf{V_{A1}}$	$Cov_{A1,2}$	$Cov_{A1,3}$	$Cov_{A1,4}$
$Cov_{A1,2}$	$\mathbf{V_{A2}}$	$Cov_{A2,3}$	$Cov_{A2,4}$
$Cov_{A1,3}$	$Cov_{A2,3}$	$\mathbf{V_{A3}}$	$Cov_{A3,4}$
$Cov_{A1,4}$	$Cov_{A2,4}$	$Cov_{A3,4}$	$\mathbf{V_{A4}}$

(B)

	Adult age (yr^3)	Fork length (mm)	Adult weight ($\sqrt{g}$)	Spawn date (ln[Julian d])	Growth rate ($mm[ln(d)]^{-1}$)
Adult age (yr^3)	**251.4**	1705.7	143.1	0.046	575.0
Fork length (mm)	1705.7	**6258.3**	688.0	0.524	874.8
Adult weight ($\sqrt{g}$)	143.1	688.0	**1082.7**	0.041	88.4
Spawn date (ln[Julian d])	0.046	0.524	0.041	**0.002**	0.009
Growth rate ($mm[ln(d)]^{-1}$)	575.0	874.8	88.4	0.009	**102.7**

provides a clear genetic framework for detecting past and future responses to selection events, permitting the incorporation of evolutionary approaches in forecasting. Second, it is possible to summarize large amounts of both empirical and simulated data and therefore to describe changes in complex phenotypes over time. Third, the multivariate selection gradient $\boldsymbol{\beta}$ provides a means of estimating the strength of selection and determining whether different traits experience similar levels and types of selection (Kingsolver and Pfennig 2007). This gradient is thus of considerable interest in evolutionary studies and has significant potential in calculating harvest or natural selection in fisheries studies.

Estimation of genetic and phenotypic covariance matrices (***G*** and ***P***) for traits of interest is a challenging but necessary step in characterizing correlated traits and identifying evolutionary opportunities and constraints. The approach depends on knowledge of the relatedness between individuals in a population. Insufficient sampling can lead to large standard errors in estimates of V_A and Cov_A and limit the number of traits that can accurately be incorporated in ***G*** (Lynch and Walsh 1998). These aspects may reduce the utility of ***G*** in studying phenotypic evolution; however, careful consideration of experimental design using sufficient steps to estimate variances and covariances of specific traits reduces the need for very large sample sizes (McGuigan 2006).

Recently, computational and theoretical advances have made empirical studies increasingly feasible. Most of our knowledge on how accurate ***G*** will be in predicting evolutionary response in natural populations is based on theory, on comparative studies between species and populations (Phillips and Arnold 1999; Steppan *et al.* 2002) and on artificial selection experiments involving a single pair of quantitative traits that covary (Roff 2007a). Here, we briefly review the state of this knowledge.

The reliability of the multivariate quantitative genetic approach in predictive studies is dependent on the stability of ***G***, ***P*** and s over the period of interest (Phillips and McGuigan 2006). In the short term, this condition is often (but not always) met for ***G*** in natural populations (Jones *et al.* 2003) and depends on the form and intensity of selection (Roff 2007a). However, strong selection or genetic drift over even a relative short period (perhaps hundreds of generations) could alter ***G*** and ***P*** considerably, with important implications for future evolution. Both factors can in theory produce similar evolutionary changes in ***G***, although selection is expected to produce non-proportional changes in the phenotype, while changes due to drift will be random (Roff

2000). Recent analytical approaches permit comparisons between ***G*** matrices empirically derived from divergent populations and go beyond asking simply whether matrices are different to postulating how they differ (Phillips and Arnold 1999). With this information, it is easier to discriminate between different evolutionary hypotheses for differentiation, such as the relative roles of selection and drift. However, additional theory is needed to determine how ***G*** might evolve in response to ecological variation (Roff 2000). Another assumption required for most multivariate analyses is that ***G*** is independent of covariation between phenotypic variation and fitness, and selection is considered to be stabilizing toward some peak in fitness (Hellmann and Pineda-Krch 2007). It is not clear if these conditions are always met.

As ***G*** and ***P*** evolve over the long term, some interesting patterns are expected. One hypothesis is that ***G***, and to some extent ***P***, will become aligned to selection over the long term (Lande 1980; Cheverud 1984; Arnold 1992; Arnold *et al.* 2001). In the short term, if selection acts to erode positive genetic correlations with respect to fitness, then we might expect ***G*** to become transiently misaligned to the line of least selective resistance, resulting in an evolutionary path with considerable curvature as a phenotype approaches a local fitness peak (Fig. 2 depicts a bivariate case). Schluter (1996) assumed that ***G*** stays constant, and thought that adaptive evolution might tend to proceed along the direction of maximum genetic variation (the principal axis, g_{max}, of the genetic covariance matrix, ***G***); deviation from this path reflects a discrepancy between the optimal and the probable evolutionary trajectory. However, as g_{max} could itself evolve, it is not clear how much of a constraint ***G*** imposes on long-term adaptation. Arnold *et al.* (2001) asked whether adaptation tends to follow genetic or selective paths of least resistance. In the latter case, evolution will tend to follow the principal axis, ω_{max}, of the fitness matrix, ω, or the width of the local selection 'surface.' It can be difficult to distinguish between these two alternatives (Arnold *et al.* 2001). The key point is that in either case, the evolutionary path taken depends to some degree on the architecture of genetic variation. However, the primary constraint imposed on evolution by ***G*** may in fact be the rate of adaptation, as determined by curvature in the evolutionary path up the slope of fitness, rather than along a more direct trajectory.

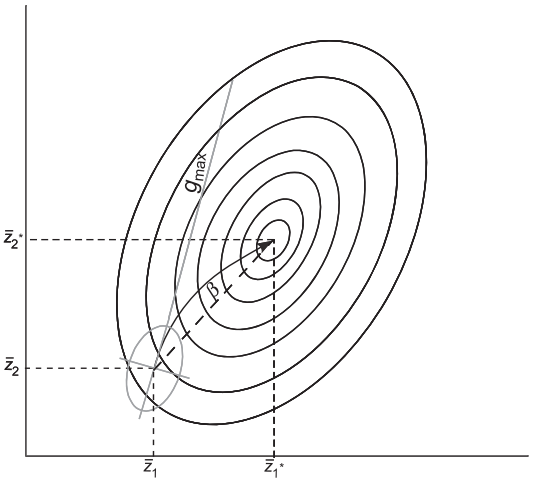

Figure 2 Orientation of the ***G*** matrix involving a pair of phenotypic traits (z_1 and z_2) toward a local fitness optimum. ***G*** is indicated by the gray oval below and to the left of the peak of fitness, encompassing the mean bivariate phenotype ($\bar{z}_1$, $\bar{z}_2$). The optimal phenotypes are $\bar{z}_1^*$ and $\bar{z}_2^*$. The principal axis of ***G*** (axis of greatest genetic variation) is g_{max} and the steepest ascent up the slope of fitness is $\boldsymbol{\beta}$, the bivariate selection gradient. Because g_{max} generally does not equal $\boldsymbol{\beta}$, evolution tends to follow a curvilinear path toward increasing fitness (even if peak fitness is stable). The evolutionary path taken depends on the architecture of genetic variation, represented by ***G*** and g_{max} and its relationship to the selection gradient. The primary constraint imposed on evolution by ***G*** is probably often the rate of adaptation, as determined by the curvature in the evolutionary path up the slope of fitness. Equations to estimate mean fitness and the selection gradient can be found in Hellmann and Pineda-Krch (2007).

Artificial selection experiments indicate that quantitative genetic approaches are successful at predicting evolutionary response in the first 10–15 generations (Roff 2007a). However, if bivariate directional selection is 'antagonistic' to the principal axis of genetic variability (i.e. when the direction of selection is not in line with the genetic correlation between traits, but acts to reduce its value with respect to fitness), responses in the correlated traits often depart considerably from prediction. The discrepancies have yet to be adequately explained, but Roff (2007a) identified six possible reasons: incorrect initial estimates, the non-genetic effect of maternal environment, genetic drift, asymmetry in gene frequencies, the nature of multivariate selection applied, and functional constraints. The multivariate approach relies on a simple additive genetic model that ignores interactions among

alleles within loci (dominance), among loci (epistasis) and between genotype and environment, and assumes a large number of underlying genes each with small effect on the traits of interest. The influence of shared environmental experience and maternal effects on phenotypic expression might be ignored or confounded in estimating genetic parameters. These factors can all misconstrue the true nature of the variation exposed to selection, or in the case of dominance and epistasis, can modify genetic variation in ways that are difficult to predict. Therefore, there is an urgent need to identify the underlying mechanisms that lead to deviations from predicted response, and attention should be paid to future experimental designs to reduce possible sources of error.

It is still not clear how accurately the multivariate breeders' equation can predict evolution in wild populations in all situations. The rich theory of life-history evolution awaits more comprehensive testing, especially over longer time scales. However, some analyses affirm that negative genetic correlation between traits plays an important role in determining how genetic variation, as represented by ***G***, provides opportunity and constraint for short-term evolution (McGuigan 2006), and that multivariate approaches show promise over short-term evolutionary scales. ***G*** is a simple representation of a complex genetic-phenotypic relationship, but it is the best representation we have. It will be even more useful when the critical details of this relationship are illuminated by expanding empirical studies, and linking expression at the level of the individual locus to the manifestation of phenotypic variation (Stern 2000).

Molecular approaches in evolutionary genetics

A practical approach to studying the evolution of quantitative traits would be to develop a mechanistic description of the molecular basis of the trait. Needless to say, this task is not trivial, because it involves identifying the genetic loci underlying the trait, examining the interactions between these loci, determining the relationship between the loci and phenotypes, testing the relationship between phenotype and fitness in a given range of environments, and developing analytical approaches to manage complex data sets that integrate all of this information. However, implementing a mechanistic approach is becoming increasingly practical following the dramatic expansion of molecular methods. Here, we briefly examine recent innovations in this field; it is not the purpose here to provide a full overview of these approaches, as this task has been performed admirably in a number of recent reviews (Vasemägi and Primmer 2005; Ellegren and Sheldon 2008). Rather, we concentrate on key conceptual issues associated with the identification of loci underlying quantitative traits, and examine how approaches may be implemented in non-model organisms, such as some fish species.

Statistical approaches to quantitative genetics typically assume that expression of complex traits involves a large number of loci of small and equivalent effect (the 'infinitesimal' model, Bulmer 1983). As a mechanistic approach is developed, it is important to identify the loci that encode these traits and to assess the relative contributions of variation at these loci to phenotypic variation. While it is clear that many of these loci are protein-coding genes, there is also substantial evidence that non-coding regions and regulatory regions play a role. In fact, there is some debate about the relative importance of regulatory and protein categories in phenotypic evolution (Hoekstra and Coyne 2007; Wray 2007). Structural variation, too, can be extensive even within a species (Clark *et al.* 2007; Kidd *et al.* 2008) and can have significant impact on fitness (Kashi and King 2006; Cooper *et al.* 2007). These facts have some bearing on how researchers may prioritize detection of functionally important loci in non-model organisms.

The most direct way to detect functional variation at the level of DNA is through sequencing (Fig. 3.1). Given dramatic improvements in sequencing technologies (Hudson 2008), it is not difficult to envisage a future where it is possible to generate whole-genome information on every organism (Hauser and Seeb 2008), if needed. Here, analytical approaches used in model organisms will facilitate rapid implementation in non-model organisms, but even when this goal is possible, it is likely that population-level analyses will be conducted with technologies that target specific polymorphic regions, such as single nucleotide polymorphism (SNP) or oligonucleotide microarrays (Fig. 3.2). Until then, researchers have adapted and will continue to adapt approaches used in organisms whose genomes have been sequenced. As examples, tests for modes of selection can be performed by examining rates of change in synonymous vs. non-synonymous sites (Fig. 3.1; Nielsen 2005) or by determining whether known regions of the genome

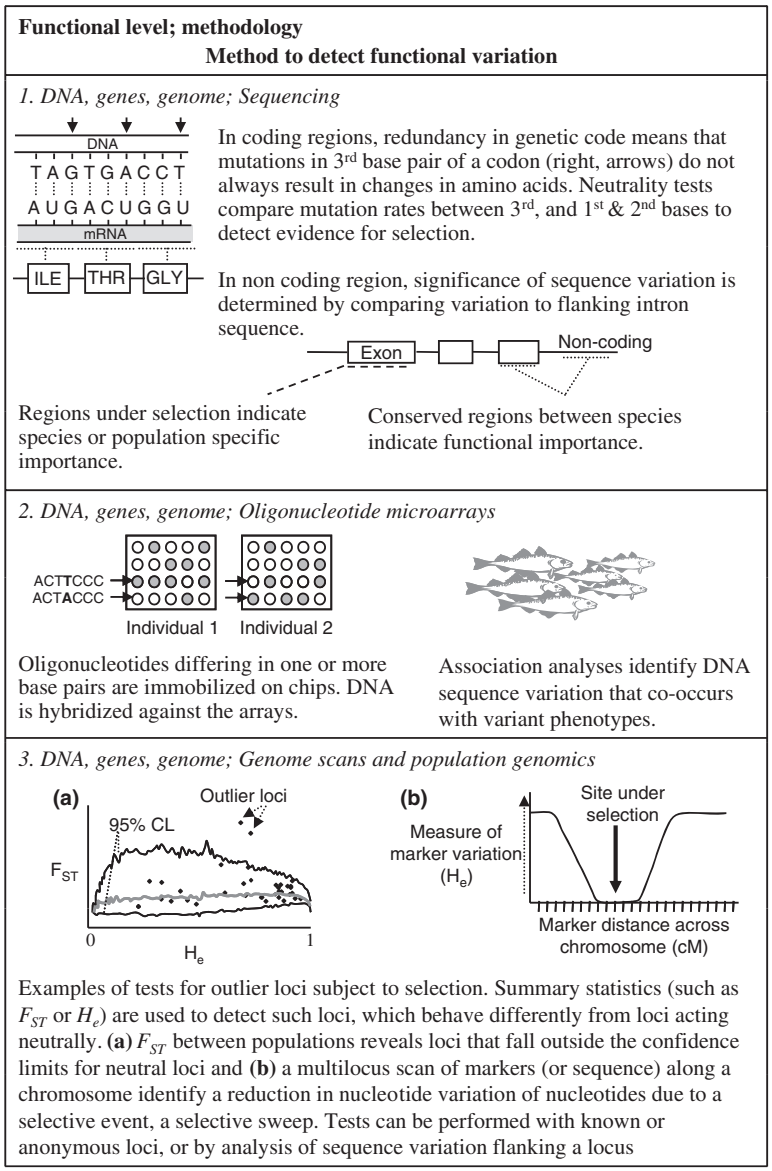

Figure 3 Summary and brief descriptions of six major types of molecular genetic methods useful for detecting functional variation that can be applied in fish species. Explanations have been simplified and are not mutually exclusive; many of the technologies are being used to address different aspects of the same questions. For example, QTL mapping can involve any pedigree in which markers and traits segregate. H_e, heterozygosity and F_{ST}, a measure of population divergence.

have undergone a selective sweep (Fig. 3.3; Storz 2005; Sabeti *et al.* 2006). Although whole genome sequences will facilitate a more comprehensive overview of the full extent of this type of variation, there is substantial scope for similar studies in non-model organisms using sequences from specific loci (Ford 2002; Salzburger *et al.* 2007), markers linked to quantitative trait loci (QTL, Fig. 3.4; Rogers and Bernatchez 2005; Stinchcombe and Hoekstra 2008; Mäkinen *et al.* 2008), expressed sequences (Väsemagi *et al.* 2005) or even with anonymous markers that may be later characterized by sequencing (Luikart *et al.* 2003; Mäkinen *et al.* 2008). Unfortunately, many of these tests are limited to situations where selective effects can be discriminated from genetic drift and where significant recombination has not occurred between the marker and the locus under selection (De Kovel 2006).

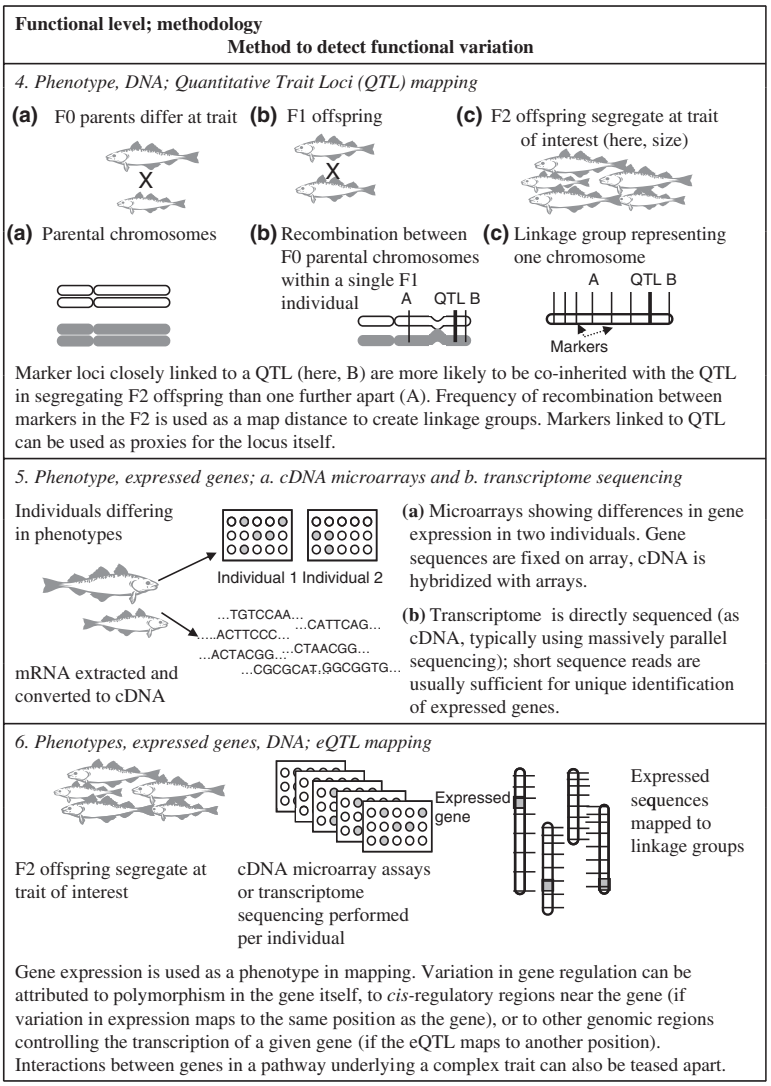

Figure 3 Continued.

An overemphasis on tests for loci that have undergone selection might ignore much of the standing variation on which future selection may act. Building a complete understanding of the link between the phenotype and the genotype will reduce this risk. Even in model organisms, this task is complex and involves many of the '-omics' disciplines aimed at organizational levels above the genome (Koonin and Wolf 2008). In non-model organisms, techniques aimed at linking the phenotype with variation at the genetic level are broader in their searches and, in the case of QTL mapping (Fig. 3.4; Danzmann and Gharbi 2001), make no assumptions or inferences about whether the underlying loci are coding or regulatory in function. Surveys of population-level variation in expressed sequences, the transcriptome (Fig. 3.5; Whitehead and Crawford 2006b; Gresham *et al.* 2008), provide a measure of variation at coding loci without emphasizing the evolutionary forces acting on those loci, and approaches such as eQTL mapping (Fig. 3.6; Jansen and Nap 2001) facilitate an understanding of how coding and regulatory regions interact to produce a given phenotype. It is clear, then, that the effective development of molecular genetic tools for the study of the evolution of complex traits in non-model organisms will depend largely on tactical approaches to detecting that variation. In species with limited

genomic resources, it is important to strike a balance between simplicity in detection method and maximizing the information that a chosen approach will provide.

One useful step that researchers can take is to prepare for a future when improvements in technology and comparative analyses (Sarrapoulou *et al.* 2008) will facilitate sequencing of all fish genomes of interest. If we assume that these technologies will increasingly move towards automation and core facilities (Hauser and Seeb 2008), then it is vital to concentrate on the biology of the organism itself and to develop resources that will bridge the gap between the genotype and the phenotype. This step will involve judiciously selecting study systems that have unique evolutionary histories that might be responding to evolutionary forces in different ways, and developing research populations in which phenotypes of interest are segregating. For example, studies aimed at detecting loci under selection are typically comparative in nature; that is, the genomes or genes of populations found in different environments are typically surveyed for evidence of non-neutral change. If this work is conducted within a phylogenetic framework, then it would be possible to gain an understanding of how recent this change might be. Such studies are further strengthened if independent populations have undergone similar evolution for the same trait: parallel evolution. If the same loci respond to selection, then it might be assumed that they may play a key role in future evolution. However, it is also important to acknowledge that a phylogenetic framework has limitations. Depending on stage of divergence, it may be difficult to discriminate signatures of selection from demographic processes such as genetic drift. Steps to correct this difficulty will depend largely on marker type (De Kovel 2006; Yang 2007).

As another example, research on many model organisms has benefited from inbred lines in which genotypes and phenotypes are fixed; crosses between these lines provide powerful approaches to identifying the link between genotype and phenotype. Unfortunately, few such lines are available in most fish species. However, crosses can be performed between individuals with different life history traits, because evolution has presumably acted to foster the differences between these forms. The ability to generate clonal lines in fishes through gynogenesis and androgenesis can increase the rates of inbreeding and serve as a means to 'bank' these genetic resources (Komen and Thorgaard 2007). However, even when such lines are created in fish species, only a few traits are typically measured at a time. Efforts to measure all possible phenotypes in available crosses will maximize the information that limited resources may be expected to provide. These measurements should be aimed at morphological, physiological, life history and behavioural characters, and include approaches that integrate gene expression data (Schadt *et al.* 2005) in order to gain a full appreciation of the interactions comprising gene networks underlying complex traits. Most systems do not have significant resources that will facilitate evolutionary studies at the molecular level, but it is important to start developing genomic tools and research populations in anticipation of technological changes in the field.

Integration of statistical and molecular approaches in quantitative genetics

The future of both of the disciplines that we have described thus far is in their integration; statistical quantitative genetics and population genetics will be the future analytical framework for loci underlying complex traits. Integration permits, at least in principle, exploration of prominent questions in adaptive evolution of fishes. These questions include characterizing the relationship between genetic and phenotypic variation within and among populations in characters that affect fitness; determining the evolutionary consequences of small population size, inbreeding and interbreeding among distinct populations; exploring how life histories respond to directional selection, such as size-selective harvest or hatchery domestication; and decomposing the genetic architecture of fitness traits. There are already several ways in which the two approaches are currently being integrated and a number of key facts have been learned from these attempts.

Evolution in wild populations using pedigree data

The first example of the integration of the two approaches is in the application of statistical methods to estimate evolutionary parameters such as selection differentials, variances and covariances, and response to selection in wild populations. This task is possible if sufficient pedigree information is available (Garant and Kruuk 2005). In many cases, this latter goal can be achieved using highly variable molecular markers (Pemberton 2008).

Generating a pedigree of wild populations produces a wide range of relationships, rather than the simpler case comprising full- or half-sibling or parent–offspring relationships that are used in many controlled laboratory or farm settings. The preferred approach to analyzing such data sets is through the application of the 'animal model' (Kruuk 2004; Postma and Charmantier 2007). The animal model is a linear model that decomposes observed variation among individuals into genetic and environmental components by relying on the phenotypic similarity among relatives. However, it is not limited to one level of relatedness typical of laboratory experiments, and is a mixed effects model that can incorporate both fixed and random effects. Fixed effects are explanatory constants that affect the mean of the distribution, while random effects permit the partitioning of remaining variances into components that can be attributed to any grouping factor. As examples, fixed effects might include age, sex or environmental variables; random effects would include individual breeding values (the average effects of a parent's genes that determine the mean genotypic value of its offspring). It is therefore possible to estimate the additive genetic variation of a given trait from these values, as well as the genetic correlation between traits, after accounting for the effects of fixed factors. There are caveats to the interpretation of the parameters estimated from animal models (Kruuk and Hadfield 2007; Wilson 2008). However, their application to wild populations has become increasingly possible, because of increases in large datasets comprising several generations, reliable parentage assignment using molecular markers, and improvements in computational methods (Kruuk and Hill 2008). These advances mean that key questions related to evolution in general and anthropogenic effects in particular are now feasible. It is difficult to overstate the importance of these studies; it is a widely held view that evolution of complex traits in wild populations can only be fully understood within the framework of quantitative genetics (Roff 2007a).

There are several significant lessons that have been learned from estimating quantitative genetic parameters in wild populations. Given that h^2 is a ratio between the additive and phenotypic variances ($h^2 = V_A/V_P$), convention states that this parameter will vary between laboratory and wild environments because the denominator is expected to increase in more variable environments. Meta-analyses of large data sets have both supported (Weigensburg and Roff 1996) and found no evidence for this conclusion (Carlson and Seamons 2008). A review of wild pedigree studies has shown that habitat quality (defined by whether the environment is favourable to a trait; Hoffmann and Merilä 1999) can affect the heritability of a trait, increasing when the environment is favourable (Charmantier and Garant 2005). This finding is significant because heritability measures the opportunity for selection. The result therefore implies that the ability to adapt to an unfavourable situation, such as exposure to a novel environment or to anthropogenic disturbance, might be reduced. Remaining on a similar theme, the response to selection of known magnitude is often readily predicted in controlled laboratory environments, but less so in wild situations. In practice, accuracy is dependent on the ability to predict multivariate responses (Merilä *et al.* 2001; Blows 2007; Roff and Fairbairn 2007). As we pointed out earlier, response is far less predictable if selection acts in a different, rather than the same, direction as the multivariate correlation (Merilä *et al.* 2001; Blows 2007; Roff and Fairbairn 2007). Despite these limitations, there are a growing number of wild pedigree studies that have successfully measured the action of selection at the individual and population level and have discriminated environmental from evolutionary change (Charmantier *et al.* 2006).

In reality, there are few long-term pedigreed populations available for evolutionary studies; and even within this group, there is a taxonomic bias towards mammal and bird populations (Postma and Charmantier 2007; Kruuk and Hill 2008). However, these studies have provided a realistic assessment of the current limitations in studies of this nature, and point towards issues that should be considered in future research (Garant and Kruuk 2005; Kruuk and Hill 2008) especially in fishes. Simply, there are philosophical, design and power issues associated with pedigree-based research. There is a tendency, for example, to focus on those traits that are simple to measure. In fishes, in particular, these are the traits that are measurable when individuals are captured, typically in the adult and pre-spawning stages. This outcome means that several key life history stages may not be observed, and also raises difficulty in evaluating correlation between traits expressed throughout an individual's life history. Undetected correlation and unmeasured selection can result in unexplained evolutionary

responses (Merilä *et al.* 2001). Statistical models that are inadequately defined because not all variances, including environmental variance, are incorporated can result in an overestimate of the additive genetic variance (Kruuk and Hadfield 2007). In many fish species developing a comprehensive sampling of a pedigree may be a challenge, because populations are large and many putative parents and offspring may not be sampled. On the other hand, several fish species produce large families and have relatively high survival rate, thereby providing greater statistical power for estimating genetic variances and covariances than do many terrestrial species. Therefore, we feel strongly that the application of pedigree-based studies should not be avoided in fish species because of these difficulties, rather that these caveats should be carefully considered in ongoing and planned experiments. Such studies have already been successfully used to estimate heritability of reproductive traits and early juvenile growth in different habitats in Atlantic salmon (*Salmo salar*, Salmonidae; Garant *et al.* 2003) and to examine the stability of selection over several generations in steelhead (*Oncorhynchus mykiss*, Salmonidae) populations (Seamons *et al.* 2007). Pedigree-based studies have much to offer in understanding the evolutionary consequences of natural and human-induced disturbances in fish populations.

Evidence for local adaptation and spatial structure in quantitative traits

It is likely that spatial structure will be poorly correlated between putatively neutral molecular genetic markers and quantitative traits or QTL. Studies of the pattern among these different measures of variation are accumulating, but for fishes these have tended to focus on first-generation crossbreeding among closely related populations in taxa that are amenable to intensive closed culture. In a meta-analysis of consequences of interbreeding between fish populations (McClelland and Naish 2007), it was found that fitness outcomes of one or two generations of interbreeding between populations that were distinct at neutral markers were generally difficult to predict. The authors concluded that measurement of adaptive divergence at quantitative traits might be better suited at identifying the consequences of gene flow on fitness than molecular genetic distance estimates. However, comparisons between these two measures can be highly informative.

A powerful approach to determining whether specific quantitative traits demonstrate local adaptation is to compare measures of genetic diversity at neutral loci measured using molecular approaches (F_{ST}) to those at quantitative traits (Q_{ST}; Spitze 1993). Both measures rely on measuring the portion of total diversity that is explained by among-population diversity; where F_{ST} is based on differences between allele frequencies at neutral loci, Q_{ST} is based on partitioning V_A. The degree of similarity between the two measures will depend on the form and strength of selection that is acting on the trait; if the traits are under strong divergent selection Q_{ST} should exceed F_{ST}, while a lower Q_{ST} may be attributed to convergent selection. F_{ST} and Q_{ST} have been found to be weakly correlated across a broad range of taxa (McKay and Latta 2002; Leinonen *et al.* 2008); however, some published estimates of Q_{ST} appear to reflect phenotypic and non-additive variation rather than additive genetic variation (Merilä and Crnokrak 2001; Goudet and Buchi 2006; Leinonen *et al.* 2008). There are also recognized biases in comparisons between F_{ST} and Q_{ST}, although these biases are correctable (Whitlock 2008).

A number of studies have used F_{ST} and Q_{ST} comparisons to detect adaptive evolution in fishes. For example, directional selection was shown to occur in small populations of grayling (*Thymallus thymallus*, Salmonidae; Koskinen *et al.* 2002), where genetic drift would be expected to be the dominant evolutionary force. Maternal components of early life history traits were shown to be under directional selection in brook trout (*Salvelinus fontinalis*, Salmonidae; Perry *et al.* 2005a). The challenge in these types of studies is to select markers and traits with an appreciation for the underlying assumptions. For example, it is often unknown whether phenotypes that are compared between populations have arisen through selection on the same genetic loci. There are several other assumptions that might not be met. Working with F_1 progeny of wild resident and anadromous steelhead from Alaska, Thrower and Hard (in press) found that while there was little evidence that adaptive divergence between these forms exceeded divergence through drift over ~20 generations (multilocus G_{ST} derived from 12 loci was similar to Q_{ST} at four traits, smoltification at age 2, maturation at age 2, growth rate between age 1 and 2 and size at age 2, ~ 0.030), the differences in survival in the wild marine environment between these forms were

substantial. Over four broods, progeny of resident parents survived at 15–20% the rate of progeny of anadromous parents. Clearly, the relationship between the quantitative traits measured and overall fitness was weak or considerable adaptive changes can arise in the wild after only little genetic differentiation; both factors may have affected the results.

Can molecular approaches forward multivariate quantitative genetic analyses?

Evolutionary science has yet to fully reconcile evolution in ***G*** with the ability to forecast phenotypic change (Turelli 1988; Kirkpatrick *et al.* 2002; McGuigan 2006). As we mention earlier, evolutionary models based on ***G*** assume that all genetic change is due to additive variance and covariance – that is, dominance and epistasis are negligible. However, it is highly likely that interactions between alleles at a locus and between alleles at different loci contribute to phenotypic evolution. Further, some alleles contribute unequally to phenotypic expression; for example, it has been argued that variation at regulatory genes has potentially more complex and far-reaching effects on expression of life history than variation at structural genes (Wray 2007). Therefore, if the loci underlying a quantitative trait can be characterized, then it is possible to study the proportional contribution of specific alleles to a given phenotype (the effect size) as well as measure the size and direction of any allelic interactions. Such an understanding can contribute to the development of theory underlying the multivariate breeders' equation and improve accuracy in predicting evolutionary change (Phillips and McGuigan 2006). To date, attempts to characterize ***G*** have involved the identification of QTL that are closely associated with phenotypic variation. QTL analyses can be useful precisely because they can identify candidate loci underlying phenotypic variation without knowing the underlying genetic details.

Many QTL experiments in fishes and other organisms have shown that quantitative traits may be encoded by few loci of large effect (Robison *et al.* 2001; Mackay 2004; Nichols *et al.* 2007; Albert *et al.* 2008). However, it is not yet clear how applicable many QTL experiments are to outbred populations (Roff 2007a), where current theory assumes that quantitative traits are encoded by a large number of additive loci of small effect. First, most QTL experiments have used inbred lines or crosses between few families, and individuals are maintained in cultured environments where environmental variance is reduced. It is likely that information on variant alleles typical of outbred populations would not be detected in these experiments and therefore their relative contribution to population level additive genetic variance would go unmeasured. Second, theory suggests that more QTL are detected with greater sample sizes, and the effect size explained by any one locus should decrease with an increase in the number of detected loci (Beavis 1998). Many QTL experiments to date have limited sample sizes and therefore reduced power to detect all QTL underlying a trait; generalizations about the distribution of effect sizes in natural populations have yet to be made (Roff 2007a). Third, the effect size at a given QTL might also be explained by the genetic background into which lines are crossed (e.g. Perry *et al.* 2003) and are expected to diminish in large populations (Roff 2007a). Finally, experimental evidence has shown that epistatic interactions can be extensive (Carlborg and Haley 2004), including in fishes (Danzmann *et al.* 1999; Perry *et al.* 2003; Nichols *et al.* 2007). It might be important to incorporate this variance in evolutionary models; there is some empirical evidence based on QTL that shows that epistatic variance can cause a larger response to selection than predicted for a single additive locus (Carlborg *et al.* 2006). In conclusion, QTL analyses have been fairly restricted in the information that they provide to statistical analyses to date, a result of the limitations associated with existing experiments. This is not to say that QTL approaches are not important in themselves; they have made very useful contributions in identifying regions of further interest and in testing the significance of genetic background on effect size, and they may contribute further to this question as the number of studies increases.

Where molecular approaches can most assist quantitative genetic analyses is in determining whether similar phenotypes are a result of selection on the same loci, an assumption in multivariate approaches. There are several studies in fishes that have tackled this question (Colosimo *et al.* 2005; Derome and Bernatchez 2006; Derome *et al.* 2006; Roberge *et al.* 2006; Shapiro *et al.* 2006). For example, repeated selection on the same gene has led to parallel evolution in plate morphology in stickleback (*Gasterosteus aculeatus*, Gasterosteidae; Colosimo *et al.* 2005), two rapidly growing Atlantic

salmon aquaculture strains derived from different sources showed evidence of selection on some of the same genes (Roberge *et al.* 2006), and parallel evolution in lake whitefish (*Coregonus clupeaformis*, Salmonidae) ecotypes involved parallelism in gene transcription (Derome *et al.* 2006). There is no doubt that further molecular characterization of the loci underlying traits will continue to add to our understanding of statistical approaches; in particular, in identifying the number of alleles at a trait-determining locus and in characterizing the effect sizes associated with epistasis and dominance in outbred populations.

Can multivariate approaches forward the molecular understanding of quantitative traits?

Gene expression produces a range of phenotypes (variation in transcription rates), and differences in expression levels between individuals can be explained by both environmental and genetic variation. Therefore, these data can be analyzed using a mixed model approach (Churchill 2002) – the same statistical framework described earlier for the analysis of quantitative traits in wild pedigrees. Where the application of quantitative genetic approaches becomes complicated is in describing the interactions between individual genes; these interactions can be modelled using the same variance–covariance framework as that described by a $\boldsymbol{G}$ matrix, but demonstrating statistical significance is difficult. A simpler approach would be to use principal components analyses (Roff 2007a).

Emergent technologies, such as microarrays or rapid sequencing of the transcriptome, offer a means of generating expression data that can be coupled with pedigree information, although the associated expense would be prohibitive in many cases. One needs to keep in mind that expression data is often specific to tissue type, life history stage and environment, thus adding to the costs of developing a comprehensive understanding of the genetic variation underlying quantitative traits. Researchers working on fishes in particular have proved highly inventive in addressing some of these limitations. For example, evolution by natural selection was demonstrated by partitioning variation in the transcriptome in natural populations of killifish (*Fundulus heteroclitus* Fundulidae) and gulf killifish (*F. grandis*) within a phylogenetic framework (Oleksiak *et al.* 2002); while much of the variation was correlated with evolutionary distance, some variation might have been attributed to adaptation. In a second example, variation in gene expression was correlated with a temperature gradient in killifish (Whitehead and Crawford 2006a). In other studies, different evolutionary forms of the same species were compared to detect variation in their transcriptomes; for example, 'territorial' and 'non-territorial' male cichlids (*Astatotilapia burtoni*, Cichlidae; Hofmann 2003), 'dwarf' and two 'normal' limnetic forms in lake whitefish (Derome and Bernatchez 2006; Derome *et al.* 2006, 2008) and morphs adopting different reproductive tactics in Atlantic salmon (Aubin-Horth *et al.* 2005). A comparison of two different selected lines in Atlantic salmon aquaculture to their source populations revealed that many of the same loci had been selected for rapid growth (Roberge *et al.* 2006). However, the separation of environmental and genetic variation was only possible in four of the studies (Derome and Bernatchez 2006; Derome *et al.* 2006, 2008; Roberge *et al.* 2006). By integrating quantitative genetics and a transcriptome scan of two populations of Atlantic salmon separated by six generations, it was possible to estimate the h^2 in gene expression of different clones and to utilize Q_{ST} to identify those genes that had responded to directional selection (Roberge *et al.* 2007), therefore providing insight into the biochemical pathways through which molecular variation results in phenotypic variation.

Looking to the future, molecular genetics will progress to the level where full descriptions of networks of interacting genes will be provided. It is our opinion that while population genetic analyses are useful for understanding the properties of single loci, the best way to describe gene networks will be within the framework of quantitative genetics, as these approaches permit the partitioning of environmental and genetic variances and take into account gene interactions (Bergman and Siegal 2003; Roff 2007b). There will no doubt be an improvement in statistical approaches, but the concepts will remain fundamentally the same.

Application of quantitative genetics to the management of fish populations

It is often asked how fish populations might cope with the challenges presented by natural and anthropogenic factors in the environment, and how we might manage such populations to reduce

these effects. A meta-analysis showed that rates of phenotypic change associated with certain anthropogenic sources of selection were stronger and more abrupt than those associated with natural selection (Hendry *et al.* 2008). The authors concluded that much of this change might be explained by phenotypic plasticity, but their results also suggest that some types of human-induced selection may outpace the ability of some populations to adapt to it. In the management of fish populations, scientists are increasingly pointing to fishing and climate change as two significant sources of human-induced selection. Here, we review these two areas as case-studies to demonstrate where quantitative genetic approaches can contribute to the field.

Fisheries-induced evolution

Fishing can impose selection on life history traits expressed in fishes in the aquatic environment that are key to fitness, including size, growth, age and size at maturation and migration, and reproductive timing. Despite decades of information on catch statistics, exploitation rate, and trends in abundance and life history, most of this information is biased toward a few commercially important species taken largely from marine waters near developed countries (Hutchings and Baum 2005). As a result, there is considerable taxonomic, geographic and habitat-related bias in the information (Fenberg and Roy 2008), and our understanding of the direct genetic effects of fishing and their implications for viability remains remarkably meagre. In most cases, the available data are represented by phenotypic trends in age and size and their association with fishing rates or patterns (Hard *et al.* 2008). The necessary ingredients for an accurate evaluation of the *genetic* effects of fishing are estimates of the selection intensity (the selection differentials S) on key traits such as size at age and age at maturation, and measures of genetic variance or heritability underlying these traits. These estimates are seldom reported or are assumed to take certain values based on published estimates for other populations.

A few studies have estimated the intensity of selection resulting from fishing. Estimates of selection differential are often negative (indicative of selective mortality affecting fish with the largest phenotypic values, typically the larger fish) and often vary considerably among populations and between years. For example, a study on a 61-year dataset for Bristol Bay, Alaska sockeye salmon (*O. nerka*) found that selection intensity has varied considerably over time, but has generally declined in more recent years (Kendall 2007). Studies based on single traits in a range of fish species have similarly found that selection differentials vary depending on population and year (Handford *et al.* 1977; Ricker 1981; Law and Rowell 1993; Sinclair *et al.* 2002; Hindar *et al.* 2007; Hilborn and Minte-Vera 2008) and in some cases, on sex (Hamon *et al.* 2000). However, most estimates of fishing selection have not been standardized by phenotypic standard deviations, which makes direct comparisons among studies (and traits within studies) difficult. The estimates that are available generally appear to be relatively weak, predominantly less than ± 0.5 phenotypic standard deviations, which is somewhat less than the few estimates of natural and sexual selection differentials that have been reported (Pacific salmon *Oncorhynchus*; Fleming and Gross 1994; Hamon and Foote 2005; Ford *et al.* 2008).

Despite the lack of unambiguous evidence for fisheries-induced evolution in any particular case, there appears to be little doubt that fishing has caused evolutionary change in several exploited species (Jørgensen *et al.* 2007; Kuparinen and Merilä 2007; Fenberg and Roy 2008; Hutchings and Fraser 2008). The important practical questions are what sort of adaptation this has produced, whether such change has increased risk of collapse, and what factors limit recovery. Several scientists have identified the critical role of size and age at maturation in determining how such evolution will play out in exploited populations. Hard *et al.* (2008) argued that the relationship between age and size at first maturation is critical in determining the form of adaptation to fishing. If a variable environment leads to variable growth opportunity, and first maturation is affected primarily by size, selective fishing can lead to evolution of increased growth rate and reduced size and age at first maturation. On the other hand, if first maturation is affected primarily by age, size selective fishing will tend to reduce growth rate and increase age at first maturation (Hard *et al.* 2008).

Most fishes with variable age-structure tend to follow the former pattern. It is possible that persistent patterns for many species in reduced size and age at first maturation may not have resulted from changes in the marine environment or in population demography only, although it remains difficult to tease apart the evolutionary effects of fishing from other factors. Jørgensen *et al.* (2007) claimed that

fishing-induced evolution is the simplest explanation for many of these patterns and that it is no longer questionable that such evolution is occurring – the question is about the rate of genetic change and its consequences for life history and resilience. Kuparinen and Merilä (2007) were more circumspect about the evidence for fishing-induced evolution, but they called for more careful monitoring and empirical analysis to detect such effects.

The potential consequences of removing fish with particular phenotypes (especially larger and older fish) from the breeding pool, while not ascertained for most specific cases, are predictable in general. The demographic effects of size-selective fishing with selection against larger, older individuals will tend to be adverse because of their selection for rapid growth, earlier maturation and reduced reproductive effort on average (Roff 1991). In addition to evolution, phenotypic plasticity can be an important component of response to selective pressure, including selective fishing mortality. It might help to mask genotypic variation from selection or generate phenotypes that selection can act upon (Ghalambor *et al.* 2007). Teasing apart the genetic from plastic responses to fishing has generally been treated with regression-based analyses (Ricker 1981; Rijnsdorp 1993; Ricker 1995; Morita *et al.* 2001) or analyses using probabilistic maturation reaction norms (PMRNs, Heino *et al.* 2002; reviewed in Dieckmann and Heino 2007). Neither approach is completely effective in discriminating between these possibilities. In particular, the growing reliance on PMRNs, which estimate the probability of maturation primarily as a function of age and size, to detect fisheries-induced evolution is of concern (Hard *et al.* 2008) because while they can help to discriminate much of the influences of growth and mortality from other sources of variation on trends in maturation, they are not themselves sufficient evidence of genetic change (Dieckmann and Heino 2007; Kraak 2007; Marshall and McAdam 2007; Wright 2007).

Quantitative genetic analysis of phenotypic change provides a more direct means of determining the direction and rate of evolution under fishing (Law 2000, 2007), but it does require reasonable estimates of genetic and environmental components of variance (Hard *et al.* 2008). In a series of studies exploring the applicability of multivariate quantitative genetics to fisheries management, **G** matrices parameterized from real populations of Chinook salmon (*O. tshawytscha*, Salmonidae; e.g. Table 1) have been used to examine the possible consequences of fisheries-induced evolution. This species is a strong test subject, because its anadromous life history and ability to home to natal spawning grounds means that populations are discrete compared to most harvested species, their life history traits are readily characterized during freshwater life history stages, and it is straightforward to create the necessary pedigrees to accurately partition V_A and Cov_A from other variances. Earlier efforts to examine the effects of size selective harvest showed that modest reductions in size, age and growth rate are possible under strong directional selection; that the response is governed by the size and direction of correlation with other traits; and that factors such as harvest size, lower size threshold and the influence of natural selection can all affect the phenotypic response (Hard 2004). However, it is not clear how these changes affect fisheries yield. A model that integrated the multivariate breeders' equation with population viability analysis (Hard *et al.* in press) indicates that life history adaptations can reduce future catch and abundance under constant exploitation rates that employ a fixed minimum capture size threshold. Such adaptation can take considerable time, however – several to many generations. Finally, use of an age-structured model in which length at different ages were treated as correlated traits was used to explore the impact of different harvest scenarios on the evolution of Chinook populations (Eldridge 2007). The major findings from this latter study showed that there are strategies than can reduce or even avoid fishery-induced evolution; for example, reducing the proportion of fish harvested, targeting only those fish that are maturing and preferentially using threshold upper size limits over slot limits. Although these models make several simplifying assumptions, they provide the basis for empirical testing, because it is possible to recreate pedigrees of harvested populations of salmon using molecular techniques to measure multivariate selection differentials and responses to selection. Quantitative genetic analyses also have an important role to play in retrospective analyses; regression-based analysis with genetic models has been shown to improve the power of trend analyses (Swain *et al.* 2007).

Molecular genetic studies have not tackled the evolutionary effect of harvest selection directly. However, a growing number of QTL analyses have provided insight into the genetic architecture of complex traits that may respond to fishery-induced

evolution. If two traits are genetically correlated, then one or more QTL underlying one trait can be expected to map to the same linkage group position as the other. Although most QTL studies in fishes cannot discriminate between pleiotropy (one locus encodes two or more traits) and linkage (two separate loci are located close to each other on the chromosome) because the existing genome maps are not sufficiently dense, the results do warrant close examination. QTL underlying morphological traits such as length, weight and condition factor map to the same linkage group position in a number of fish species (Reid *et al.* 2005; Wright *et al.* 2006), and it is reasonable to assume a correlated response in these traits. Given that the debate in this area has focused on the likely relationship between size and age at maturity, it is interesting to note that in rainbow trout *O. mykiss*, several QTL for age at maturation have mapped to the same linkage group position as some body mass QTL (Martyniuk *et al.* 2003) and one to a QTL involved in embryonic development rate (Sundin *et al.* 2005). Our understanding of the genetic architecture of life history traits will improve as information on fish genomes and gene expression increases, but it is clear that there is a genetic basis to the correlations observed between many phenotypic traits that likely respond to harvest. Future molecular research directed at this specific question might compare gene expression at different time points between 'harvested' and 'unharvested' populations originally derived from the same genetic backgrounds. If transcriptional rates are treated as phenotypes, they may be partitioned into variance components corresponding to specific life history traits or correlated traits in order to elucidate the genetic architecture of phenotypes that likely respond to harvest selection. Estimates of sequence differences between the genes expressed by the experimental populations will identify those genes that have diverged, and will provide tools for the future monitoring of allele frequency changes in exploited populations.

The evidence for fisheries effects on life history evolution in exploited fishes is still too dependent on retrospective analyses of phenotypic trends that cannot completely isolate confounding factors from genetic response. Although more careful empirical work and analysis is necessary to assign trends to fishing effects in particular cases, there is a general agreement that fisheries management should incorporate evolutionary considerations to improve sustainability of exploited populations (Jørgensen *et al.* 2007; Law 2007; Fenberg and Roy 2008; Hard *et al.* 2008; Hutchings and Fraser 2008). Hutchings and Fraser (2008) suggested that the focus should be on evaluating the conservation and socio-economic consequences of such evolution. Indeed, whether fishery managers would seriously entertain adjusting management strategies from those intended to maximize yield to those intended to maintain genetic, phenotypic, and ecological variation (Fenberg and Roy 2008) seems to be the pertinent political challenge. Doing so would require clearer guidance from evolutionary biologists. Future approaches should be predictive in nature, and here we highlight growing efforts to implement quantitative genetic approaches. Significantly, multivariate models based on empirical data can readily integrated into fisheries forecasting. Proactive strategies based on evolutionary genetics could significantly help to reduce, ameliorate or potentially even reverse evolutionary changes, albeit at lower rates than those induced by high exploitation (Law 2000).

Adaptation to climate change

Fish populations are likely to require complex adaptations to respond effectively to climate change. Selection will be imposed by changes in several climate-related factors as well as an increase in CO_2 concentration itself (Reusch and Wood 2007), and therefore responses in photoperiodicity, temperature stress tolerance and traits that affect dispersal are predicted. The genetic basis of variation in some of these traits is now being investigated in some model species, facilitating the implementation of candidate gene approaches for non-model species (Reusch and Wood 2007).

In the aquatic environment, modifications in temperature, salinity, wind and current patterns will produce changes in currents and surface layers of water bodies, which in turn will likely alter patterns of larval dispersal with consequences for survival and gene flow. Acidification of water bodies will result in altered habitats. New local adaptations might arise, but will such adaptations be sufficient to permit local persistence? Little empirical work has investigated the effects of climate warming (or, for that matter, cooling) for fishes, but a few evolutionary models have explored potential consequences. Most incorporate an infinite alleles approach under directional selection or stabilizing selection around a moving optimum (Pease *et al.* 1989; Lynch *et al.*

1991; Lynch and Lande 1993; Gomulkiewicz and Holt 1995; Lande and Shannon 1996; Boulding and Hay 2001; Kingsley *et al.* 2004; Hellmann and Pineda-Krch 2007), (see Fig. 4 for a simple depiction involving a single trait; see Hellmann and Pineda-Krch 2007 for an exploration of bivariate phenotypic evolution). These models differ in their details (e.g. deterministic vs. stochastic, discrete time vs. continuous time, truncation vs. directional or stabilizing selection), but they all attempt to determine whether a population's rate of adaptation will be rapid enough to cope with projected change in the environment, or whether extinction will ensue.

In their stochastic discrete-locus model, for example, Boulding and Hay (2001) found that the rate of adaptation could be rapid, but depended heavily on population size and productivity, trait heritability and the strength of selection, but less on the mutation rate or the degree of environmental stochasticity. Small populations with low fecundity were especially at risk because of the synergistic effects of demographic and genetic stochasticity on productivity. In general, it appears that the critical rate of adaptation is limited by effective population size (N_e), genetic variability, and the rate of environmental change (the rate of change in the phenotypic optimum) that determines the selection differential. Small populations in regions affected more strongly by climate change are probably at higher risk than larger populations in regions with more modulated changes in physical environment, especially if dispersal is sufficient to respond to environmental change.

What important characteristics of marine populations are likely to be altered by climate change and how will these patterns alter resilience? In an assessment of the impacts of climate change since the last glaciation on adaptation of marine fish such as herring (*Clupea harengus*; Clupeidae), flounder (*Platichthys flesus*; Pleuronectidae) and cod (*Gadus morhua*, Gadidae) in the Baltic Sea, it was found that prominent adaptations in these fishes included increased reproductive rates and improved performance of larvae in environments with reduced and more variable salinity and dissolved oxygen (Ojaveer and Kalejs 2005). Periods of increased salinity tend to boost abundance and spatial distribution. Such dynamic conditions, these authors concluded, have increased habitat heterogeneity and have probably fostered adaptations to local conditions and led to adaptive differentiation. Whether continued warming will augment these trends or increase them in other, less confined, marine regions is not clear. The scale of local adaptation may be different (perhaps larger) in such

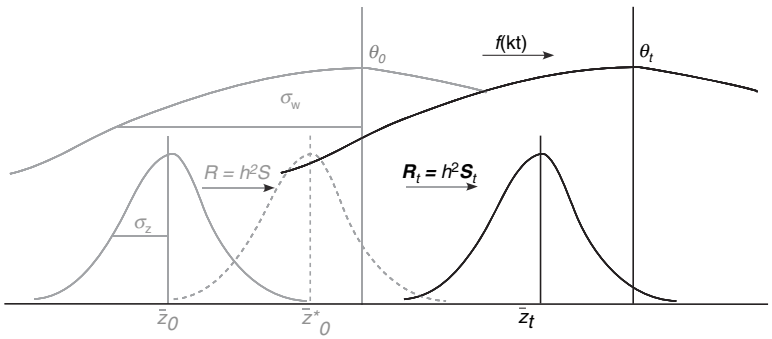

Figure 4 Directional selection acting on a single phenotypic trait with a mean away from the selective optimum (θ_0), as might occur under climate change (Grey). Under typical conditions, selection acts to move the phenotypic mean ($\bar{z}_0$, with standard deviation σ_z) closer to the optimum (θ_0) to a point $\bar{z}^*_0$; the degree to which it moves (the response, R) depends on the strength of selection (the selection differential, S, the difference between the mean of individuals after selection but before reproduction and the mean before selection, $\bar{z}_0$) and the heritability (h^2) of the trait. The distribution of fitness with optimum has breadth σ_ω, with larger values indicating weaker selection (Black). With a systematically moving optimum that is expected under environmental change such as climate warming, selection acts to move $\bar{z}_0$ toward the optimum θ_0, which is now moving at a rate k per unit time t. Without considering important complications like demographic and environmental stochasticity, phenotypic plasticity, and genetic drift, whether $\bar{z}^*_0$ can track changing θ_t depends essentially on whether the cumulative rate of response R_t equals or exceeds kt. For each population, there will be some critical rate of environmental change that exceeds the population's ability to adapt.

regions. Bradshaw and Holzapfel (2008) have argued that for most organisms in temperate regions, the primary consequences of climate change will be temporal shifts in the expression of key life history events, including timing of reproduction, migration and dormancy. They predicted that climate warming will have a larger effect on ameliorating winter low temperatures than on increasing summer high temperatures, resulting in milder winters and longer periods of relative warmth during an extended growing season.

Evolutionary responses in life-history traits to environmental change are likely for many organisms (reviewed by Hendry and Kinnison 1999; Reznick and Ghalambor 2001). As already discussed, most traits probably have sufficient genetic variation to respond to strong selection. Others, such as temperature-dependent larval development, migration timing and habitat choice, might also be influenced by phenotypic plasticity. These plastic responses can be adaptive, but our understanding of how genetic change and plasticity and evolutionary changes combine to influence fitness is still rudimentary (Kinnison and Hairston 2007; Gienapp *et al.* 2008; Kinnison *et al.* 2008). Climate change might also produce conflicting selection pressures in different life stages, which could interact with plastic changes in complex ways.

Adaptation to climate change shares several characteristics with adaptation to fishing and other anthropogenic factors; what differs primarily is the form (and potentially intensity) of selection. For example, we can expect that climate warming will affect growth rate and potentially alter the seasonal timing of maturation in many species. If reproduction is favoured by directional selection toward an earlier seasonal optimum, evolution toward earlier reproductive timing will ensue if rates of development and maturation are rapid enough. The consequences of such evolution for persistence and life history variability are of considerable interest to conservation biologists and fishery managers. One possible deleterious outcome of selection for earlier timing of reproduction is reduced fertility and smaller propagule size – a result with clear implications for individual fitness and population productivity.

The population structure of many marine fishes is typically believed to be weak and there is some question as to whether local adaptation associated with climate change might be expected in such environments, given high rates of gene flow. However, analyses that compare neutral genetic markers and candidate loci under selection in marine fishes are challenging this hypothesis (see Hemmer-Hansen *et al.* 2007; Larsen *et al.* 2007; Pampoulie *et al.* 2008a,b; see Hauser and Carvalho 2008 for a review). For example, differential gene expression in North Sea and Baltic Sea flounders that were reciprocally transplanted in experimental facilities that mimicked natural salinities implied local adaptation, despite little evidence for differentiation at neutral markers (Larsen *et al.* 2007). Temperature and salinity gradients within the Baltic might explain differentiation in a heat-shock protein, Hsc70 (Hemmer-Hansen *et al.* 2007). Adaptation in gene expression could be common in other marine organisms with low levels of population subdivision. Physical gradients that might affect dispersal could also be very important in maintaining population structure and fostering local adaptations in the marine environment, and these gradients are likely to be altered under climate change.

Some insight into the genetic correlation between traits that might respond to climate change has been provided by a range of QTL studies in fishes. In a species that has anadromous and resident forms, steelhead and rainbow trout, growth rate and condition factor QTL map to the same position as metrics associated with smoltification (Nichols *et al.* 2008), a key physiological process involved in marine migration. In rainbow trout, body size and spawning date QTL (O'Malley *et al.* 2003) and temperature tolerance and fork length QTL (Perry *et al.* 2005b) are located at the same linkage group position. In tilapia (*Oreochromis* sp., Cichildae), QTL linked to stress response and body weight map together (Cnaani *et al.* 2004) and there is evidence for physical linkage between temperature tolerance and size (Cnaani *et al.* 2003). We repeat our caveat that co-localization of QTL to similar map positions does not imply pleiotropy – however, the results are intriguing because it appears that growth-related traits are genetically correlated to a number of life history and physiological traits that might be expressed during temperature stress. Further studies examining the direction of these correlations will provide a more complete understanding of the likely outcomes of the evolutionary response to environmental factors influenced by climate change.

As is the case for other evolutionary challenges, heritability and genetic correlation in key life history traits such as timing of reproduction and

growth rate might pose a limit to rates of adaptation to climate change. For example, if ***G*** is not oriented to permit rapid evolution along a performance line of least resistance (Fig 2; *sensu* Arnold 1992), the rate of adaptation could easily be outpaced by relatively rapid environmental change. If ***G*** can change in orientation to maximize evolvability, the rate of adaptation should accelerate and increase the probability of persistence.

Future directions in the application of quantitative genetics to the evolution of fishes

Several decades ago, the application of quantitative genetics to natural fish populations might have appeared intractable or limited to a few select species. This perspective may still be true for many species, but the list of informative evolutionary studies in fishes is growing. We return to our earlier argument that researchers and funders should anticipate improvements in technology and statistical approaches in ways that will facilitate their research in all species of interest. This perspective calls for developing a strategic approach to addressing some of the key issues facing the management of fish populations.

Fish species run the gamut of life history strategies that, as examples, range from high to low fecundity, rapid to slow growth, simple or complex age-structures, or short or long lived. Therefore, it is inevitable that short lived species that are readily manipulated at reproduction have and will be used as models for evolution in other species. In fishes, the selection of species whose genomes have been sequenced has been driven separately by motives underlying medicine, aquaculture or evolution and these interests rarely intersect. Therefore, most of the genome projects to date have been centred on species of interest to medicine such as zebrafish (*Danio rerio*, Cynprinidae; Sun *et al.* 2008) and medaka (*Oryzias latipes*, Adrianichthyidae; Kasahara *et al.* 2007), although increasingly many genome projects are being established in aquaculture species (Liu 2007; Wenne *et al.* 2007). Occasionally, species such as stickleback have been targeted for genomic studies on the basis of their interest to evolutionary studies alone (Kingsley *et al.* 2004). These developments mean that as genomic information is generated in each of these species, the information can be used to study their wild counterparts or to phylogenetically related species. As we stated earlier, the future limitations will be in our understanding of biological complexity, in our ability to identify and measure relevant phenotypes, and in our access to appropriate research populations. Advances that better integrate analyses of multivariate phenotypes with improved mechanistic understanding of gene expression are central to breaking down these barriers. In addition, it will be possible to generate important new hypotheses about opportunity and constraint for adaptation by developing dynamic models that can integrate evolutionary and demographic factors. These models can be used to evaluate phenotypes involving suites of ecologically relevant characters, as well as testing underlying assumptions about variation in gene expression and the effects of evolutionary forces on genetic architecture.

It is important to recognize that the expansion in genomics has led to the point where large pedigree sets in natural fish populations are increasingly feasible (Anderson and Garza 2006), thus facilitating the implementation of evolutionary studies under many wild conditions. Here, the limitation will be the ability to study evolutionary change across several generations, because the phenotypes of populations are not usually tracked, DNA material is rarely collected over generations, and selection differentials are infrequently measured. This problem might be addressed by integrating tissue sampling into ecological collections for those species that are closely studied for monitoring reasons, and by measuring as many environmental parameters as possible. An emphasis will probably be placed on testing those species whose populations are discrete, have short generation times and are readily accessible during their spawning migrations, although it is entirely feasible that long-lived and late maturing species might be studied using pedigree-based cohort analyses. Alternatively, the evolution of those species that are less amenable to pedigree-based studies will likely be studied using comparative genomic approaches.

We find it encouraging that many key advances in the field of evolutionary genetics have occurred in fishes. While it can be argued that some other species are of far higher research priority, many fish species have several advantages as study organisms in quantitative genetics, as they are readily tagged and measured, are easily reared, have large family sizes and several species return to known spawning grounds. We have no doubt that their continued importance to medicine, fisheries, conservation and

aquaculture will facilitate their inclusion in forthcoming genetic studies, where they will provide important future insights into adaptive evolution.

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