MOLECULAR APPROACHES IN NATURAL RESOURCE CONSERVATION AND MANAGEMENT

Recent advances in molecular genetics and genomics have been embraced by many scientists in natural resource conservation. Today, several major conservation and management journals are using the "genetics" editors of this book to deal solely with the influx of manuscripts that employ molecular data. The editors have attempted to synthesize some of the major uses of molecular markers in natural resource management in a book targeted not only at scientists but also at individuals actively making conservation and management decisions. To that end, the text features contributors who are major figures in molecular ecology and evolution – many having published books of their own. The aim is to direct and distill the thoughts of these outstanding scientists by compiling compelling case histories in molecular ecology as they apply to natural resource management.

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Molecular Approaches in Natural Resource Conservation and Management

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Preface

The world would be a wonderful place if our natural resources (e.g., forests, fish, and wildlife) needed no management and conservation was not a concern. In a world with a global human population approaching 7 billion and where most developed nations overconsume these resources, however, conservation is a concern and management is necessary for sustainable use. Historically, natural resource management strategies were determined by the collection and interpretation of basic field data. Today, as challenges to the sustainability and conservation of our natural resources arise, managers often need data that cannot be acquired using conventional methods. For example, a natural resource manager might want to know the number of successful breeders in a population or if genetic variation was being depleted because of a management practice. Traditional field craft alone cannot directly address such questions, but the answers can be determined with some precision if the field work is coupled with modern molecular genetic techniques.

Molecules can enlighten us about biological attributes that are virtually impossible to observe in the field (Avise 2004). Parentage analysis is one such arena in which genetic data can inform management practices (DeWoody 2005), but there are a host of others. For example, molecular data have revealed deep evolutionary splits in stocks at one time thought to be homogeneous. This finding has concomitant management implications (Hoffman et al. 2006). Similarly, molecules can enlighten us about biologies that are virtually impossible to observe in the field, such as pollen flow (Hamrick, this volume) or the physiology of migration (Nichols et al. 2008).

Recent advances in molecular genetics and genomics have been embraced by many scientists in natural resource conservation. Today, several major conservation and management journals (e.g., *Journal of Wildlife Management, North American Journal of Fisheries Management, Plant Breeding Reviews*) are now using "genetics" editors to deal solely with the influx of manuscripts that employ molecular data. We have attempted to synthesize some of the major uses of molecular markers in natural resource management in a book targeted not only at scientists but also at individuals actively making conservation and management decisions. To that end, we have identified contributors who are major figures in molecular ecology and evolution; many have published books of their own. Our aim has been to direct and distill the thoughts of these outstanding

scientists by compiling compelling case histories in molecular ecology as they apply to natural resource management.

Clearly, we hope this book will appeal to academics interested in conservation genetics, molecular ecology, and the quantitative genetics of wild organisms. We think this book could be used as an educational tool – as a text for graduate ecology/genetics courses but also, perhaps, in advanced undergraduate courses. Furthermore, we hope this book will be useful to audiences in natural resource management, education, and research by clarifying how genetic approaches can be used to answer resource-related questions.

ABOUT THE EDITORS

Our collective expertise spans from molecular population genetics in the wild to genomics and quantitative genetics of managed or cultured species. We all study the genetics of natural resources, however, and we find that similar issues arise in wildlife, forestry, and fisheries. For example, when the forest geneticists began asking how many sires contributed pollen to a nut-bearing hardwood tree, it turns out that fisheries geneticists had already studied this problem from the perspective of a male fish guarding a nest full of developing embryos, and they had created computer programs to estimate the number of parents contributing gametes to a nest (DeWoody et al. 2000). Another such intersection of research across disciplines lies in the study of genetic processes in small populations; the same conceptual and analytical approaches being used to elucidate the genetic consequences of wildlife reintroductions (Latch & Rhodes 2005) are employed to evaluate genetic diversity in hardwood tree species subjected to severe habitat fragmentation (Victory et al. 2006). Our desire to produce a book stems from our mutual interests in understanding how molecular genetics can be used to inform and improve natural resource management.

In addition to our research interests, we teach several courses that directly pertain to this book. These courses include *Conservation Genetics* (DeWoody), *Molecular Ecology and Evolution* (DeWoody), and *Evolutionary Quantitative Genetics* (Nichols). Furthermore, several of us (DeWoody, Michler, Rhodes) have served as "genetics" editors for conservation and management journals, including *Journal of Wildlife Management, North American Journal of Fisheries Management*, and *Plant Breeding Reviews*.

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individual chapters and boxes, and we trust that this book has been enhanced by their efforts.

This volume was largely possible because of the financial and logistical support of the Department of Forestry and Natural Resources at Purdue University. In particular, the department sponsored an October 2008 meeting at Purdue where many of the book contributors congregated for three days of scientific discourse and fellowship before finalizing their respective chapters or boxes.

Our own research programs have been supported by a variety of organizations, including the National Science Foundation (DeWoody, Bickham, Michler, Nichols), the U.S. Department of Agriculture (DeWoody, Michler, Nichols, Rhodes, Woeste), the State of Indiana (DeWoody, Michler, Rhodes), the National Oceanic and Atmospheric Administration (Bickham), the Great Lakes Fishery Trust (DeWoody, Nichols), and the U.S. Forest Service (Michler, Woeste). We thank them all for investing in science.

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6 Association genetics, population genomics, and conservation: Revealing the genes underlying adaptation in natural populations of plants and animals

Krista M. Nichols and David B. Neale

INTRODUCTION

Understanding the genetic basis of complex adaptive traits is key to understanding how natural and anthropomorphic factors have influenced and will influence the shape of genetic diversity and trajectory of evolution in natural populations. Complex adaptive traits are quantitative traits – those that vary on a continuous scale, and even more generally, are sometimes defined as traits that are expressed as a function of products from multiple genes (Falconer & MacKay 1996; Roff 1997; Lynch & Walsh 1998). Although classical quantitative genetics has revealed the genetic basis to numerous morphological, physiological, and life history traits in plants and animals, the actual genes (loci) and allelic variation with loci underlying key functional differences among organisms remain unknown. Understanding the genes involved in species- and population-level diversity can provide important tools (i.e., genetic markers) for resource managers that are charged with conservation, management, and restoration of natural populations. In this chapter, our examples and review are focused on non-model, non-domesticated organisms as it is the diversity in natural populations, shaped by the natural processes of evolution, with which natural resource managers are most concerned.

Population genetics has undoubtedly been one of the most important fields in the conservation, management, and restoration of native plant and animal species. Together with ecological and life history information, "neutral" genetic markers, or those mirroring the neutral demographic processes of natural populations, are important tools for the delineation of management units or evolutionary significant units for conservation and management. Loci that have been shaped by natural selection, in the process of adaptive population divergence, can however exhibit levels of differentiation markedly different than neutral loci (Leinonen et al. 2008; Vali et al. 2008; Nosil et al. 2009). Until recently, understanding the genetic basis of complex traits has been limited to model

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Figure 6–1: Schematic representation of LD among genetic markers, genes, and a causal mutation. Gray and white contiguous blocks represent haplotype blocks with significant LD, and within those blocks are genes. Detecting significant genotype–phenotype associations will depend on LD between genetic markers and the causal mutation. In this case, the causal mutation (gray star) is in LD with three markers (black stars). Note that the causal mutation is not itself surveyed in the study, but by linkage with markers, a significant genotype–phenotype association would be observed with the markers typed in the study.

organisms, which are easily reared in a laboratory or common garden environment, and for which genetic and genomic resources were available. With the expansion of genomics and statistical genetics in the last decade and numerous genetic tools capable of surveying large numbers of genetic markers or genes in the genome, the identification of candidate gene and genome regions underlying ecologically relevant traits is now possible. The identification of genes and allelic variation at genes functionally linked to ecologically variable phenotypes is tractable for even non-model species, and results from association genetics studies have great promise in providing added resolution in defining units for conservation and management. These studies, together with classical quantitative genetic approaches, reveal that genes or markers linked to genes underlying adaptive population divergence can give very different signatures of population divergence, and that, even in the face of low to moderate gene flow observed at neutral genetic markers, natural selection can maintain adaptive population divergence at genes underlying ecologically relevant traits (Leinonen et al. 2008).

In all cases, the ability to identify genes or genome regions associated with adaptive population differentiation or within population diversity relies on linkage disequilibrium (LD), also called gametic phase disequilibrium, between markers surveyed and the causal mutation(s) (Fig. 6–1). LD is the nonrandom association of alleles at different genes or loci (Slatkin 2008). LD can arise between loci that are physically unlinked as a consequence of population genetic processes such as genetic drift, population subdivision, population bottlenecks, inbreeding, and epistasis; the magnitude of LD among physically linked loci is a function of the amount of recombination among linked loci (see Slatkin 2008 for a review). The concept of LD is an extremely important one in association genetics as the extent of LD between observed markers and the causal genetic variant partially responsible for the observed phenotypic variation will largely dictate the power of different methods in revealing genes or genome regions associated with the trait of interest. If LD is high over long stretches of the genome, fewer markers are needed for association genetics, but the likelihood of identifying the genetic variant responsible for phenotypic variation is much lower. If LD is low across the genome or is found in only short haplotype blocks, many more markers will be needed to detect associations across the whole genome; however, with shorter blocks of LD across the genome, the task of identifying the causal genetic variant becomes much easier. In rare cases is the causal mutation responsible for the phenotypic variability surveyed or observed in initial analyses in non-model organisms.

Table 6–1. A sampling of major reviews of the methods and utility of association genetics

Topic	Phenotype? quantified?	Pedigree/ crosses?	References
Population genomics & neutrality tests Tests for signatures of natural selection	No	No	Nielsen 2001, 2005; Luikart et al. 2003; Schlotterer 2003; Storz 2005; Vasemagi & Primmer 2005; Thornton et al. 2007; Li et al. 2008; Stinchcombe & Hoekstra 2008
LD mapping Genotype–phenotype association studies in populations of unknown pedigree	Yes	No	Gupta et al. 2005; Stinchcombe & Hoekstra 2008; Weir 2008
QTL analysis Detection of genes or genome regions associated with phenotypes of interest in pedigreed populations	Yes	Yes	Wu et al. 2002; Erickson et al. 2004; Slate 2005; Stinchcombe & Hoekstra 2008

The literature is replete with reviews of the theoretical and statistical approaches and methods used for association genetics and the identification of genes or genome regions that have been shaped by natural selection (Table 6–1). We do not intend to exhaustively recapitulate prior reviews but rather provide a general overview with relevance to natural or free-living populations, paying special attention to the advantages and challenges of these methods in non-model, non-domesticated natural or free-living plant and animal populations. We take the definition of natural population in terms of the genetic dissection of ecologically relevant traits as defined by Slate (2005), who provides an excellent overview and review of quantitative trait loci (QTL) mapping methodologies and empirical results in natural populations of animals. Slate (2005) defines a *natural population* as one that is "descended from recently sampled individuals of a non-domesticated origin" excluding "model organisms that have been reared in the laboratory for many generations." This definition is particularly important as we review the primary literature for the identification of QTL in natural populations as few association genetic studies have been conducted in un-manipulated, non-domesticated populations of organisms. Although we recognize that natural populations of model organisms have been explored, we limit our review to those species that are not long-standing model organisms (i.e., *Drosophila*, *Arabidopsis*, crops, and domesticated animals) and to those traits that have ecological significance in natural populations.

METHODS FOR DETECTING GENES FOR ECOLOGICALLY RELEVANT PHENOTYPES

Here, we detail methods that take two major approaches in the identification of genes or genome regions significantly associated with adaptive divergence

among individuals and populations. The first group of methods (quantitative genetic approaches), including LD or association mapping and QTL analyses, rely on surveys of molecular markers and measures of known phenotypes of interest. The second group of methods (population genetic approaches), called hitchhiking mapping, does not necessarily require measurement of phenotypes on all individuals but rather aims to identify molecular markers showing unusual patterns of population genetic differentiation (i.e., outliers) between populations of interest.

Quantitative genetic approaches

LD or association mapping

LD or association mapping reveals genes or genome regions that are significantly associated with specific phenotypes in natural populations of organisms of unknown relationship (see Neale & Ingvarsson 2008; Stinchcombe & Hoekstra 2008; Weir 2008 for review). LD is among the intuitively simplest of tests for genotype–phenotype associations; individuals sampled from natural populations are evaluated for their phenotype in some type of replicated genetic test, genotyped for polymorphisms in a subset of candidate genes or throughout the genome, and genotype–phenotype associations are tested in the absence of linkage mapping or known family relationships. Because family relationships and population subdivision alone can lead to false-positive associations between genotype and phenotype, ad hoc, multivariate methods are used to account for population subdivision and relatedness using a subset of "neutral" genetic markers (Pritchard et al. 2000; Yu et al. 2006; Zhao et al. 2007). These methods eliminate false-positive associations that arise simply because of population subdivision but can also eliminate true phenotype–genotype associations that covary with population subdivision. Because association mapping uses relatively simple linear mixed models, additional fixed and random effects can be incorporated into models testing for genotype–phenotype associations to account for phenotypic variation among environments, sexes, year classes, and so forth, in addition to variation occurring as a result of population subdivision (Yu et al. 2006; Stich et al. 2008; Yu et al. 2008). There are two main approaches for LD or association mapping, and these are categorized into tests for association with specific candidate genes (or candidate regions) of interest, or genome-wide tests for association.

Candidate gene approaches. For non-model organisms lacking a genome sequence or significant genomic resources, the candidate gene approach for association mapping offers more immediate and simple tests for association with phenotypes of interest. Originally devised for tests of association in complex human diseases, numerous statistical tests or approaches have been devised for tests for association between candidate gene polymorphisms and phenotypes (see Long & Langley 1999; Balding 2006 for reviews). Genes with known roles in particular suites of life history, physiological, behavioral, or morphological traits in model organisms or better-studied taxonomic groups may provide the best candidates

for similar traits in non-model organisms (Fitzpatrick et al. 2005). Even in the absence of significant genomic sequence resources, motifs in candidate genes that are conserved across taxa can be used to identify primers to isolate the homologous gene sequences in non-model organisms of interest (Krutovsky et al. 2007). Moreover, with massively parallel sequencing, candidate genes, whole transcriptomes, and whole genomes can be used for single nucleotide polymorphism (SNP) detection even in non-model organisms (Ellegren 2008). The candidate-gene approach has been particularly successful across taxonomic groups and offers the greatest promise for initial association mapping studies in non-model organisms. In some cases, genome regions identified from QTL mapping studies in controlled crosses of the same or related species would provide information on candidate regions for association studies. The disadvantage of the candidate-gene approach is that for some traits, a reasonably viable set of candidate genes is not available without pursuing genome-wide approaches such as whole genome expression or transcriptome studies.

Genome-wide association approaches. Genome-wide tests for genotype–phenotype associations are so far limited to model organisms for which significant genomic resources are available. For genome-wide tests of association, suites of markers distributed across the genome are tested for genotype–phenotype associations. In most cases, the position or order of these markers across the genome is known from linkage mapping or genome-sequencing efforts. A genome-wide scan, then, gives an overview of the patterns of genotype–phenotype associations along the chromosomes. Although deemed "genome-wide" approaches, a true whole genome approach would sample all polymorphisms at the genomic level, and this is a monumental task even in fully sequenced genomes. With LD among closely linked loci, it is not necessary to sample every polymorphism in the genome. In fully sequenced organisms, the extent of LD across the genome can be evaluated to determine, on average, the size of haplotype blocks in the genome, as depicted in Fig. 6–1. From this information, representative markers from those regions (sometimes called "tag SNPs") can be used for whole-genome approaches in LD mapping (Carlson et al. 2004). In non-model organisms, obtaining information on the size and genomic distribution of haplotype blocks across the genome is a huge undertaking in itself. In non-model organisms, the most promising approach for genome-wide association studies may come in surveying associations in large numbers of candidate genes or expressed sequences identified from transcriptome sequencing (gene-space scan).

There are a number of advantages of LD mapping in natural populations when compared to QTL mapping and population genomics approaches. First, although LD mapping can account for relatedness among individuals using neutral markers, complete and known family relationships among individuals in the sampled population(s) are not necessary as they are for QTL studies in natural populations. In many organisms, pedigrees cannot be determined directly by observation and thus rely on time-consuming and expensive efforts to reconstruct pedigree information using molecular markers (Blouin 2003; Pemberton 2008). Compared to QTL mapping in the more traditional sense of one or a few

crosses, LD mapping has the advantage of surveying many more recombinants in the population, offering finer resolution for the possible detection of the causal mutation(s) responsible for variation in phenotype. For non-model organisms with few genomic resources available, candidate-gene association mapping offers the greatest promise for tests of phenotype–genotype associations. The major disadvantage of LD mapping in non-model organisms is the time and expense required to survey sequence polymorphisms for the development of SNP markers either in few candidate genes or on a genome-wide level.

Quantitative trait loci (QTL) analysis

QTL analyses seek to identify genes or genome regions significantly associated with phenotypes of interest in known crosses or pedigreed populations of plants and animals. The application, tools, and use of QTL analysis for natural populations are reviewed by Erickson and colleagues (2004) and Slate (2005); for a comprehensive overview of design and analysis of QTL, readers are referred to Doerge and coworkers (1997) and Lynch and Walsh (1998). Briefly, the tools required for this type of analysis include individuals produced in a known breeding scheme or of known relationships in a pedigreed population, molecular marker genotypes of these progeny for markers distributed across the genome, and phenotypes of interest measured in individuals from the breeding scheme or pedigree. The observed amount of recombination between markers used for genotyping is used to order markers into linkage groups, which are used as a framework for statistical tests of genotype–phenotype associations. By observing the cosegregation or inheritance of molecular marker genotypes with phenotypes of interest within the context of this linkage map, genome regions that are significantly associated with variation in the phenotypes are identified.

The type of breeding scheme used for QTL analysis in natural populations is largely related to the question(s) of interest. In model organisms, QTL analyses are commonly conducted in progeny produced from inbred line crosses, maximizing the amount of LD between marker genotype and phenotypes of interest. For outbred populations of interest, QTL analyses are conducted in crosses between individuals with divergent phenotypes or can be conducted in pedigreed populations. For questions regarding genes involved in speciation or reproductive isolation between divergent populations, crosses made between species or populations are necessary to dissect the architecture of quantitative traits, unless a natural hybrid zone can be identified. For questions regarding genes underlying phenotypic variation within populations, although crosses between individuals with divergent phenotypes can be made, analysis in the full or partial pedigree of the population would sample more of the genetic and phenotypic diversity within the population, taking into account the genetic relationships among all pairs of individuals (Slate et al. 1999; George et al. 2000; Pemberton 2008).

There are both advantages and disadvantages in using QTL analysis compared to other methods for association genetics. The advantage of the QTL approach in known, single-generation crosses is that LD between polymorphic markers and phenotypic traits are maximized as a result of observing many fewer recombination events in a single cross when compared to multiple generations and multiple crosses in a pedigree. Because LD is maximized (i.e., gray and white

contiguous blocks of LD are longer in Fig. 6–1), many fewer markers are needed to perform QTL analysis; however, because LD is maximized, the likelihood that a QTL analysis will identify the causal mutation responsible for a proportion of the phenotypic trait variation is low. Moreover, because few individuals are selected for crossing, mutations at some loci associated with phenotypic variation may go undetected if markers linked to or the actual causal mutation are not polymorphic in the few individuals that were drawn for crosses from the larger population. As a result, crosses may not capture some of the significant causal variants for phenotypic variation that may be found if the entire population or populations are sampled. Progeny from crosses manipulated by the experimenter are generally reared and phenotyped in a laboratory or common garden, where the effects of environment can be controlled. Controlling the environment is an advantage for the detection of QTL in that trait variance due to environmental effects is minimized, but for some traits, the environment-dependent expression of the trait is an important context for studies interesting to ecologists, evolutionary biologists, and conservation biologists. In contrast, QTL analyses in pedigreed populations take advantage of the larger amount of recombination that has occurred among generations and families of individuals with different phenotypic trait values. Because of this reduced level of LD among phenotypic traits and causal mutations (i.e., gray and white contiguous blocks are shorter in Fig. 6–1) as a function of sampling more meioses in the population, QTL analyses in natural populations will require much larger sample sizes and many more markers to detect the same QTL that may have been observed in line crosses. In QTL analysis, pedigree information is directly included in tests for genotype–phenotype associations and is more accurate in defining shared coancestry among individuals than are methods used in LD mapping to account for kinship (Pemberton 2008). In both approaches, the power and precision to detect and localize loci underlying quantitative traits will depend on the number of markers chosen, the amount of recombination events or LD observed between markers, and the effect size of individual loci (Doerge et al. 1997; Lynch & Walsh 1998; Doerge 2002). Because recombination rates and LD are unique not only to species but also to specific regions of chromosomes, providing a magic number for the number of individuals and markers to choose for genome-wide approaches is not possible. Lynch and Walsh (1998) detail calculations for the numbers of individuals and markers to use in genome-wide QTL analysis with specific QTL effect sizes and desired accuracy of mapping QTL. QTL analyses in crosses made in non-model organisms in the laboratory or common garden environments are numerous, but the use of this approach in natural or free-living populations is limited to systems where the pedigree is known or can be estimated from parentage analysis using molecular markers.

Population genetic approaches

Hitchhiking mapping and outlier analysis

Population genomics is the assessment of population genetic parameters at large numbers of loci distributed across the genome, with the aim of identifying loci that have been shaped by natural selection (Schlotterer 2002, 2003; Luikart et al.

2003; Storz 2005; Thornton et al. 2007). Whereas much of the genome will reflect patterns of neutral genetic variation attributed to mutation and demographic processes, "outlier analysis" identifies loci in the genome showing unusually high or low patterns of variation among populations due to the effects of natural selection. This approach is also called hitchhiking mapping and rests on the idea that strong directional or divergent selection for an advantageous allele creates strong LD with closely linked loci, and that as an advantageous allele approaches fixation, a decrease in heterozygosity at closely linked loci will also be observed (Maynard Smith & Haigh 1974). LD around the beneficial mutation is strongest and more extensive when said mutation is a new mutation immediately acted upon by positive selection; when natural selection shapes standing genetic variation, the extent of LD of the beneficial mutation with unlinked loci will depend on the amount of neutral variation that has accumulated in the region (a function of the effective population size) and recombination (Przeworski et al. 2005). Several tests have been devised for tests of these signatures of natural selection in the genome. In all cases, population genomic tests are most powerful for detection of directional or divergent selection on new mutations, which instantly creates LD at linked neutral sites. Detecting signatures of selection on standing genetic variation is more difficult as diversity about the causal mutation is greater due to neutral evolution prior to the onset of directional selection.

Among all of the approaches reviewed herein, the tools required for population genomics are the simplest: Individuals from populations of interest are genotyped at polymorphic markers (amplified fragment length polymorphism [AFLP], microsatellite, or SNP) across the genome, population genetic parameters are calculated based on allele frequencies within and across sampled populations, and signatures of unusually high or low patterns of genetic diversity within and between populations are revealed with statistical tests. Population genetic parameters used for detection of outlier loci include: 1) F_{st} showing unusually large or small levels of population subdivision compared to most loci sampled (Lewontin & Krakauer 1973; Vitalis et al. 2001; Beaumont & Balding 2004; Beaumont 2005); 2) lnRV, which captures the natural log of the ratio of variance in microsatellite repeat number or allele sizes between populations (Schlotterer 2002); 3) lnRH, which captures the natural log of the ratio of expected heterozygosity between populations (Kauer et al. 2003); and 4) the Ewens–Watterson neutrality test, which tests for excess or deficits in expected homozygosity (Watterson 1977). Tests for outliers are made either empirically by the identification of outliers in the distributions of the population genetics parameters mentioned earlier in text, or by comparing the distribution of these test statistics to distributions of the same statistics generated by coalescent simulations under a model of neutral evolution and particular demographic scenarios (Teshima et al. 2006).

In non-model organisms, particularly organisms for which little or no genomic sequence information exists, the outlier analysis approach is among the easiest to perform as anonymous genetic markers such as AFLPs and microsatellites can readily be used. Moreover, as sequencing costs decline with the rapid development of new sequencing technologies, generation of genomic sequences in non-model organisms will become quite tractable (Ellegren 2008; see also Chapter 4 by DeWoody and colleagues). The outlier analysis approach does not require the

collection of phenotype data, a time-consuming and difficult task for particularly complex phenotypes. As with the LD mapping and QTL approaches, the ability to sample all loci in the genome for signatures of natural selection will depend on the extent of LD among closely linked loci. Unfortunately, because outliers can occur as false positives or false negatives owing to the large numbers of tests performed and possible violation of simple assumptions of demography (Simonsen et al. 1995; Teshima et al. 2006), it is necessary to follow up with candidate outliers with additional validation to determine if the region linked to the markers indeed shows patterns of sequence variation consistent with directional selection and is functionally linked to phenotypes or life history traits.

Neutrality tests with sequence or SNP data

For single or few loci, tests of neutrality are based on sequence or SNP data. In some cases, outliers identified in population genomic studies are followed up with tests for signatures of natural selection using sequence information in candidate regions, and, in others, candidate genes are used. These tests can be roughly broken down into three categories: 1) tests within and among populations of the same species ("polymorphism tests"); 2) tests among species ("divergence tests"); and 3) joint tests of population and species level variation ("joint polymorphism and divergence tests") (Nielsen 2001, 2005; Walsh 2008). In all cases, the neutral model of evolution serves as the null hypothesis. For within-species analyses, site frequency spectrum of polymorphisms or haplotype diversity is compared against neutral expectations; examples of these types of tests include Tajima's D and Fu and Li's D and F tests (Nielsen 2001, 2005; Walsh 2008). Population genetic polymorphism tests are subject to strong assumptions about population demography and often have low power compared to divergence and joint tests (Simonsen et al. 1995; Nielsen 2001, 2005; Zhai et al. 2009). Many divergence tests and joint tests evaluate whether nonsynonymous-to-synonymous substitution rates (d_N/d_S) in genes deviate from those expected under neutrality and are not subject to false positives due to demographic processes (Nielsen 2001, 2005; Zhai et al. 2009). One popular joint test is called the McDonald–Kreitman test, which evaluates the d_N/d_S ratio within and between species. Another common joint test is the Hudson–Kreitman–Aguade test, which compares sequence variation within versus between species, with the idea that within- and between-species divergence under neutral expectations will depend only on mutation rate. In most cases, tests for signatures of natural selection using sequence data use multiple tests and approaches to verify whether the null hypothesis of neutrality can be rejected. Nielsen (2005) offers an excellent review of the effects of different scenarios of natural selection (directional and balancing selection, selective sweeps) on within- and between-species variability.

Tests for neutrality on one or few loci have an obvious advantage for non-model organisms and the same advantages as candidate-gene association tests. Sequence data are readily obtainable from non-model species for few candidate loci. One limitation of this approach, as mentioned earlier, includes false rejection of the null, neutrality hypothesis due to violation of assumptions of equilibrium demography when polymorphism-based tests are used. Tests based on divergence are inherently testing hypotheses about strong or repeated selection among species,

whereas polymorphism tests within species detect recent selection. Readers are directed to Zhai and colleagues (2009) and Teshima and coworkers (2006) for excellent reviews and simulations of the power of outlier and neutrality tests for testing for signatures of natural selection.

IDENTIFICATION OF GENES UNDERLYING ADAPTIVE TRAITS: EXAMPLES IN PLANTS AND ANIMALS

Although most association genetic studies have been conducted in model organisms, the transfer of these tools to related non-model, non-domesticated, natural or free-living populations has allowed the genetic dissection of ecologically relevant traits, with potentially important implications for conservation and management application. In many cases, the real power in the identification of genes associated with ecologically relevant traits comes from combining these approaches (Vasemagi & Primmer 2005; Neale & Ingvarsson 2008; Stinchcombe & Hoekstra 2008). In the next sections, we give some examples of how these different approaches have been successful in the identification of genes and, in some cases, the causal mutations, responsible for a large proportion of phenotypic or ecotypic variability in non-model or natural or free-living populations of animals and plants.

Genome-wide association and QTL studies in animals

No genome-wide association studies have been conducted in natural or free-living populations of animals, but a few QTL studies have been published for natural or free-living populations of animal species (Table 6–2). Published QTL studies in natural or free-living populations are limited to long-term data sets derived from carefully tracked pedigrees in populations of large mammal species, namely red deer (*Cervus elaphus*; Slate et al. 2002) and Soay sheep (*Ovis aries*; Beraldi et al. 2007a,b). Linkage maps have been developed for several other free-living or natural populations and will serve as an important resource for QTL and LD mapping in those species.

Most genome-wide studies of genotype–phenotype associations for ecologically relevant traits have occurred in crosses manipulated by researchers in the laboratory, using QTL analyses (Table 6–2). These studies have identified QTL for morphological variation, behavior phenotypes (including host preference–mediating ecological speciation and mate preference), disease resistance, and other physiological or life history traits. QTL mapping, as mentioned earlier in text, is not a means to an end and rarely identifies the causal mutation(s) underlying phenotypic variation, but it provides important information on genome regions to further test for associations with phenotypes of interest using LD mapping or in tests for signatures of natural selection. In fact, QTL studies provide an important top-down approach in the identification of candidate regions and gene sets for candidate gene association and tests for natural selection (Tables 6–3 and 6–4, respectively). For example, in lake whitefish, QTL identified for growth and morphological characters in manipulated crosses between pelagic and benthic forms

Table 6–2. Examples of QTL analyses in non-model, non-domesticated animal species of ecological significance

Species	Common name	Morphology	Physiology	Behavioral	Life history & fitness
Amphibians & reptiles					
Ambystoma mexicanum	Mexican axolotl		Voss & Shaffer 2000		
Fish					
Astyanax mexicanus	Cavefish	Protas et al. 2006, 2008; Gross et al. 2009	Protas et al. 2008		
Coregonus clupeaformis	Lake whitefish	Rogers & Bernatchez 2005			
Gasterosteus aculeatus	Three-spined stickleback	Peichel et al. 2001; Colosimo et al. 2004; Shapiro et al. 2004; Albert et al. 2008; Miller et al. 2007			
Labeotropheus fuelleborni × *Metriaclima zebra*	Cichlid spp.	Streelman et al. 2003			
Oncorhynchus mykiss	Rainbow trout	Nichols et al. 2004, 2008; Zimmerman et al. 2005	Jackson et al. 1998; Ozaki et al. 2001; Robison et al. 2001; Martyniuk et al. 2003; Nichols et al. 2003, 2007, 2008; O'Malley et al. 2003; Zimmerman et al. 2004; Perry et al. 2005; Sundin et al. 2005; Drew et al. 2007		Martyniuk et al. 2003; Haidle et al. 2008
Oreochromis mossambicus × *O. aureus*	Tilapia		Cnaani et al. 2004; Moen et al. 2004		
Salmo salar	Atlantic salmon		Houston et al. 2008; Moen et al. 2005; Ozaki et al. 2005; Reid et al. 2005; Moghadam et al. 2007		Moghadam et al. 2007

(*continued*)

Table 6–2 (*continued*)

Species	Common name	Morphology	Physiology	Behavioral	Life history & fitness
Insects					
Acyrthosiphon pisum	Pea aphid			Hawthorne & Via 2001; Via & Hawthorne 2002	Hawthorne & Via 2001; Via & Hawthorne 2002
Aedes aegypti	Mosquito		Zhong et al. 2006		
Anopheles gambiae	Mosquito		Menge et al. 2006		
Anopheles gambiae × *A. arabiensis*	Mosquito				Slotman et al. 2004
Apis mellifera	Honeybee			Rueppell et al. 2004, 2006; Hunt et al. 2007	
Bombus terrestris	Bumblebee		Wilfert et al. 2007a,b		Wilfert et al. 2007b
Culex pipiens × *C. quinquefasciatus*	Mosquito				Mori et al. 2007
Heliconius cydno × *H. pachinus*	Butterfly			Kronforst et al. 2006	
Heloconius melpomene	Butterfly	Baxter et al. 2009			
Laupala paranigra × *L. kohalensis*	Hawaiian cricket			Shaw et al. 2007	
Tribolium castaneum	Red flour beetle		Zhong et al. 2003, 2005		Zhong et al. 2005
Mammals					
Cervus elaphus	Red deer	Slate et al. 2002			Slate et al. 2002
Ovis aries	Soay sheep	Beraldi et al. 2007b	Beraldi et al., 2007a,b		Beraldi et al. 2007b

Table 6–3. Summary of selected candidate-gene association studies in non-model, non-domesticated animal species

Species	Common name	Trait	Candidate genes	Reference
Amphibians & reptiles				
Ambystoma mexicanum	Axolotl	Metamorphic timing	*THRα, THRβ*	Voss et al. 2003
Aspidoscelis inornata	Little striped whiptail	Body color	*MC1R*	Rosenblum et al. 2004
Thamnophis sirtalis	Garter snakes	Tetrodotoxin resistance	*tsNa(V)1.4*	Geffeney et al. 2005
Birds				
Acrocephalus arundinaceus	Great reed warbler	Parasite load	*MHCI*	Westerdahl et al. 2005
Anser c. caerulescens	Snow goose	Plumage color	*MC1R*	Mundy et al. 2004
Coereba flaveola	Bananaquit	Plumage color	*MC1R*	Theron et al. 2001
Parus major	Great tit	Personality	*DRD4a*	Fidler et al. 2007
Passer domesticus	House sparrow	Disease resistance	*MHCIIb*	Bonneaud et al. 2006
Stercorarius parasiticus	Arctic skuas	Plumage color	*MC1R*	Mundy et al. 2004
Insects				
Bicyclus anynana	Butterfly	Eyespot size	*Distal-less (Dll)*	Beldade et al. 2002
Solenopsis invicta	Fire ant	Social & mating system	*Gp-9*	Ross & Keller 1998; Krieger & Ross 2002
Fishes				
Astyanax mexicanus	Cavefish	Body coloration	*MC1R*	Gross et al. 2009
Gadus morhua	Atlantic cod	Muscle fiber number; growth and condition; migration behavior	*PanI*	Johnston & Andersen 2008; Jonsdottir et al. 2008; Pampoulie et al. 2008
Gasterosteus aculetus	Three-spined stickleback	Body armor plates	*Eda*	Cano et al. 2006; Kitano et al. 2008
Metriaclima zebra	Zebra mbuna cichlid	Body coloration	*c-ski*[a]	Streelman et al. 2003
Mammals				
Canis lupus	Gray wolf	Coat color	*K locus*	Anderson et al. 2009
Chaetodipus intermedius	Pocket mice	Coat color	*MC1R, Agouti*	Nachman et al. 2003
Ovis aries	Sheep	Coat color	*MC1R; TYRP1*	Deng et al. 2009; Gratten et al. 2007[b]
Peromyscus polionotus	Oldfield mouse	Coat color	*MC1R, Agouti*	Mullen & Hoekstra 2008
Other invertebrates				
Mya arenaria	Soft shell clam	Paralytic shellfish poisoning resistance	*rNav 1.2a*	Bricelj et al. 2005

[a] Gene linked to causal mutation.
[b] See also case study in this chapter.

Table 6–4. Examples of population genomics and tests for neutrality in natural populations of animals

Species	Common name	No. of loci or genes studied	Marker type	Reference
Amphibians & reptiles				
Rana spp.	Frogs	1	Candidate gene	Tennessen & Blouin 2008
Rana temporaria	Common frog	Many	AFLP	Bonin et al. 2006
Birds				
Falco naumanni	Lesser kestrel	1	Candidate gene (MHC)	Alcaide et al. 2008
Rupicapra rupicapra	Alpine chamois	1	Candidate gene (MHC)	Mona et al. 2008
Fishes				
Cichlid spp.	Cichlids	Many	SNPs	Loh et al. 2008
Clupea harengus	Atlantic herring	12	Microsatellites	Watts et al. 2008
Coregonus clupeaformis	Lake whitefish	Many	AFLP	Campbell & Bernatchez 2004
Fundulus heteroclitus	Mummichog	1	Candidate gene	Powers & Schulte 1998
Gadus morhua	Atlantic cod	Many, 11	SNPs; microsatellites	Nielsen et al. 2006; Moen et al. 2008
Gasterosteus aculeatus	Three-spined stickleback	15 Many 109 1	Microsatellites Microsatellites, candidate genes Microsatellites, candidate gene	Raeymaekers et al. 2007; Makinen et al. 2008a,b; Barrett et al. 2008
Haplochromine/Tilapiine spp.	Cichlid spp.	82	Genes	Gerrard & Meyer 2007
Haplochromis spp., *Oreochromis niloticus, Astatotilapia burtoni*	African cichlids	Many	Candidate genes	Gerrard & Meyer 2007
Oncorhynchus tshawytscha	Chinook salmon	11	Microsatellite, candidate gene	O'Malley et al. 2007
Salmo salar	Atlantic salmon	14 95	Microsatellites, candidate genes Microsatellites	Vasemagi et al. 2005a,b
Telmatherina prognatha *Telmatherina antoniae*	Sailfin silversides	573	AFLP	Herder et al. 2008
Theragra chalcogramma	Walleye pollock	38	Microsatellites, allozymes, candidate gene	Canino et al. 2005

Insects				
Acyrthosiphon pisum	Pea aphid	45	AFLP, EST	Via & West 2008
Apis mellifera	Honeybee	Many	SNPs	Zayed & Whitfield 2008
Colias eurytheme	Butterfly	1	Candidate gene	Wheat et al. 2006
		1	Candidate gene	Watt 1977
Melitaea cinxia	Glanville fritillary butterfly	1	Candidate gene	Orsini et al. 2009
Neochlamisus bebbianae	Leaf beetle	Many	AFLP	Egan et al. 2008
Timema cristinae	Walking sticks	Many	AFLP	Nosil et al. 2008
Zeiraphera diniana	Larch budmoth	Many	AFLP	Emelianov et al. 2004
Mammals				
Arvicola terrestris	Water vole	2	Candidate genes (MHC)	Bryja et al. 2007
Gracilinanus microtarsus and *Marmosops incanus*	American mouse opossums	1	Candidate gene (MHC)	Meyer-Lucht et al. 2008
Oryctolagus cuniculus	European rabbit	25	Allozymes	Campos et al. 2008
Ovis dalli	Wild sheep	3	Candidate genes	Worley et al. 2006
Peromyscus maniculatus	Deer mice	18	Allozymes	Storz & Dubach 2004
Peromyscus maniculatus	Deer mice	2	Candidate genes	Storz & Kelly 2008
Peromyscus polionotus	Oldfield mouse	2	Candidate genes	Mullen & Hoekstra 2008
Peromyscus spp.	Mice	10–37	Allozymes	Storz & Nachman 2003
Peromyscus spp.	Mice	1	Candidate gene	Gering et al. 2009
Other invertebrates				
Mytilus edulis	Mussel	11	Microsatellite	Faure et al. 2008
Crassostrea virginica	Oyster	Many	AFLP	Murray & Hare 2006
Littorina saxatilis	Marine snail	Many	AFLP	Wilding et al. 2001
		Many	AFLP	Galindo et al. 2009
		14	Candidate regions	Wood et al. 2008

colocalize with markers showing signatures of natural selection (i.e., "outlier" behavior) between sympatric pairs of these morphotypes found in several lakes in Quebec (Campbell & Bernatchez 2004; Rogers & Bernatchez 2005). In three-spined sticklebacks, the colocalization of QTL to the ectodysplasin gene provided the foundation for tests of *Eda* polymorphism and signatures of natural selection in natural populations exhibiting variation in lateral plate numbers (Colosimo et al. 2005).

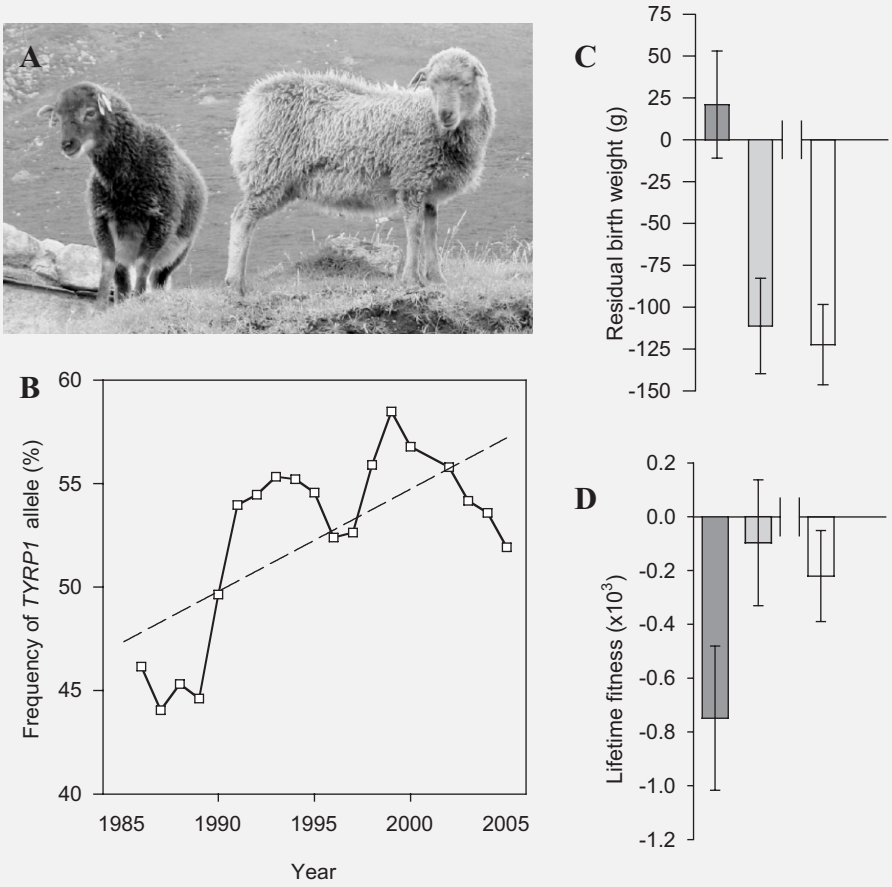
To our knowledge, no genome-wide LD or association mapping studies have yet been conducted in free-living or natural populations of animals. Important first steps for genome-wide association studies, however, include the generation of genome-wide sequence and SNP variation information, as well as examination of the extent of LD within species. In some non-model species, these resources are beginning to emerge; these resources include information on the extent of LD in wild mice (Laurie et al. 2007), red deer (Slate & Pemberton 2007), and collared flycatchers (Backstrom et al. 2006b), as well as linkage maps in wild bird populations including the great reed warbler (Akesson et al. 2007), collared flycatcher (Backstrom et al. 2006a), and zebra finch (Stapley et al. 2008).

Candidate-gene association studies in animals

The candidate-gene approach is by far the approach most used, and holds the most promise for use in non-model, natural populations of organisms. In most cases, candidate genes are chosen based on their known role for particularly morphological, behavioral, physiological, or life history traits in other taxa. Comparative genomics and identification of genes by whole-genome expression studies are also avenues for the identification of candidate genes. In non-model animal species, many candidate-gene studies have been focused on body-color polymorphism (see Protas & Patel 2008 for review) and disease resistance and mate choice as it relates to major histocompatibility complex (MHC) loci polymorphisms (Piertney & Oliver 2006) (Table 6–3). Examples include genetic polymorphism in coat color genes in mice species that are adapted to different environments (Nachman et al. 2003; Steiner et al. 2007), in hemoglobin genes in mice adapted to different altitudes (Storz et al. 2007), in color genes associated with albinism in cavefish (Protas et al. 2006), and in plumage coloration involved in mate choice (Mundy et al. 2004). Although the adaptive significance is not apparent, a gene associated with coat-color polymorphism in Soay sheep (Gratten et al. 2007) has also been identified and appears to segregate in the population with linked fitness-related traits (see Box 6 case study). In fewer cases, candidate genes are identified for further study based on whole-genome approaches such as QTL or association mapping. For example, polymorphism in the *Eda* gene found in QTL for plate morph in three-spined stickleback is associated with plate morphs in wild marine and freshwater populations (Colosimo et al. 2005; Barrett et al. 2008; Kitano et al. 2008). The fact that most candidate genes have been identified outside of whole-genome approaches is more likely due to the extensive resources and time needed to conduct a genome-wide study and to the extensive genomic resources needed to follow up with QTL studies to identify genes within QTL regions.

BOX 6: UNRAVELING COUNTERINTUITIVE EVOLUTIONARY TRENDS: COAT COLOR IN SOAY SHEEP

Jake Gratten, Alastair J. Wilson, Allan F. McRae, Dario Beraldi, Peter M. Visscher, Josephine M. Pemberton, and Jon Slate



Box Figure 6–1: (a) The two coat-color morphs in Soay sheep. (b) Increase in frequency of the *Tyrp1* T allele over a twenty-year period (linear regression, slope of +0.49%/year, $r^2 = 0.390$, $p = 0.004$). (c) Mean birth-weight differential of GG sheep (dark gray bar) and TT sheep (light gray bar), in each case relative to GT sheep, and of light sheep (white bar) relative to dark sheep. (d) Mean lifetime fitness differential of *Tyrp1* genotypes and coat-color phenotypes.

Background

Evolutionary biologists sometimes report that heritable traits under directional selection fail to evolve as predicted (Merila et al. 2001). A polymorphism for coat color in a wild population of Soay sheep (Box Fig. 6–1, a) is determined by a single nonsynonymous G → T substitution in the tyrosinase-related protein 1 gene (*Tyrp1*); GG homozygotes and GT heterozygotes have dark coats, whereas TT homozygotes are light (Gratten et al. 2007). Dark sheep are heavier than light sheep, and body size is positively correlated with fitness (Wilson et al. 2006). Therefore, it is surprising that the recessive light allele (T), which is not ancestral,

has reached a frequency of approximately 0.50 and has not declined in frequency during twenty years of intensive monitoring (Box Fig. 6–1, b). Why does coat color, which has a simple genetic basis, show a counterintuitive evolutionary trajectory?

Case Study

More than 2,500 Soay sheep living between 1985 and 2005 were typed at the *TYRP1* causative mutation, and genotype data were integrated with pedigree, life history, and body size data (Gratten et al. 2008). First, associations between *Tyrp1* and body size were analyzed using an "animal model" approach, whereby polygenic effects on body size were modeled as a random effect, independently of *Tyrp1* genotype (fixed effect). Similar models were constructed with coat-color phenotype instead of *Tyrp1* genotype. Both color ($F_{1,2201.5} = 26.03$, $p < .0001$, $n =$ 2,370) and *Tyrp1* ($F_{2,1623.1} = 8.96$, $p = .0001$, $n = 1{,}757$) explained significant variation in birth weight (Box Fig. 6–1, c) and body size later in life. Dark sheep were heavier than light sheep, and the G allele was partially dominant for body weight (such that GG $\geq$ GT $>$ TT). These findings were supported by a transmission disequilibrium test (TDT: $F_{1,421} = 4.60$, $p = .034$), a form of combined association and linkage mapping that eliminates possible causes of spurious association such as undetected population structure or admixture. Thus, the relationship between body size and *Tyrp1* is due to genetic linkage, and dark sheep really are expected to be fitter than light sheep, all else being equal.

Next, associations between *Tyrp1*/coat color and fitness were analyzed using animal models and TDTs. Color was not associated with lifetime fitness, despite the fact that dark sheep were heavier than light sheep. *Tyrp1* genotype was associated, however, with lifetime fitness (Box Fig. 6–1, d; animal model: $F_{2,1336} =$ 4.03, $p = .020$, $n = 1{,}355$). It is intriguing that fitness differences between *Tyrp1* genotypes were not those predicted by effects on body size. There was a cryptic difference between phenotypically indistinguishable homozygous (GG) and heterozygous (GT) dark sheep, with GG sheep being less fit than either GT dark sheep or TT light sheep. This association was also confirmed to be due to linkage (TDT; $F_{1,427} = 6.87$, $p = .010$, $n = 492$).

What do these results mean? The *Tyrp1* gene is associated with both body size and fitness, either directly or because it is in LD with tightly linked genes that affect the focal traits. These genes appear to act antagonistically because GG sheep are large but less fit, TT sheep carry alleles that confer small body size (but greater fitness), and GT sheep are relatively large and fit. Although body size is under directional selection, a localized negative genetic correlation in the vicinity of *Tyrp1* means that large body size alleles in this part of the genome are associated with decreased fitness. Overall, sheep carrying the T allele, irrespective of their size, are favored, which may explain why T has increased in frequency. These associations were able to be detected only when coat color genotype rather than phenotype was analyzed, due to the cryptic fitness difference between the two categories of dark sheep. The lessons from this study are that 1) an evolutionary response to selection can be modulated by local genetic correlations between linked genes, and 2) studying the underlying genotype of a trait may be

necessary to understand its evolutionary dynamics. Although the conservation genetic implications of this research are less immediate, the work does illustrate the fact that making management decisions on the basis of one trait may have unpredictable consequences on other genetically correlated traits.

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Tests for signatures of natural selection in animals

In natural animal populations, tests for signatures of natural selection have identified outlier loci associated with ecological specialization, speciation, and adaptation in a wide range of species (Table 6–4). Tests for signatures of natural selection at loci throughout the genome ("population genomics") have been one of the most rapidly developing areas for the identification of genes underlying adaptive population divergence. Because population genomics requires multiple testing and has the potential for the identification of false positives and negatives under certain selection and demographic scenarios (see *Hitchhiking mapping and outlier analysis*), the best supported evidence for true positives in outlier tests are those loci that can also be validated by linkage to QTL or by follow-up studies evaluating the identity of genes and nature of sequence variation functionally associated with traits of interest. For example, outliers identified by population genomics in sympatric ecotypes of lake whitefish are often colocalized to QTL regions for morphological and physiological differences among ecotypes (Campbell & Bernatchez 2004; Rogers & Bernatchez 2005). Outliers identifying footprints of selection in three-spined stickleback colocalize to QTL for morphotypic variation in that species (Makinen et al. 2008a). Anonymous AFLP marker loci identified as outliers among parapatric populations of *Littorina* gastropods (Wilding et al. 2001) have been used to isolate genomic sequence for finer-level sequence analysis of genes and genome regions under natural selection (Wood et al. 2008).

Genome-wide association and QTL studies in plants

Large-scale candidate gene or genome-wide association studies in plants have, until recently, been restricted to the model plant *Arabidopsis thaliana* (Zhao et al. 2007) or the domesticated plant *Zea mays* ssp. *mays* (Yu & Buckler 2006). There is an extensive literature on QTL mapping in forest trees, however (Table 6–5). We classify trees as plants from natural population versus domesticated plants because in just about every case, forest-tree QTL mapping studies begin with

Table 6–5. Summary of QTL analyses conducted in non-model, non-domesticated plant species

Forest Trees							
Scientific name	Common name	Growth	Phenology	Disease resistance	Cold hardiness	Drought tolerance	Wood property
Castanea sativa	Sweet chestnut	Casasoli et al. 2004, 2006	Casasoli et al. 2004				
Cryptomeria japonica	Japanese cryptomeria	Yoshimaru et al. 1998					Kuramoto et al. 2000
Eucalyptus globulus	Tasmanian blue gum	Marques et al. 2002; Kirst et al. 2004; Thamarus et al. 2004; Bundock et al. 2008	Bundock et al. 2008	Bundock et al. 2008			Bundock et al. 2008
Eucalyptus grandis × *Eucalyptus urophylla*	Grand eucalyptus × Timor mountain gum	Grattapaglia et al. 1995, 1996; Verhaegen et al. 1997; Marques et al. 2002; Missiaggia et al. 2005					Grattapaglia et al. 1996; Byrne et al. 1997a,b; Verhaegen et al. 1997; Kirst et al. 2005
Eucalyptus nitens	Shining gum	Byrne et al. 1997a			Byrne et al. 1997b		
Eucalyptus tereticornis	Forest red gum	Marques et al. 2002					
Fagus sylvatica	European beech	Scalfi et al. 2004					
Larix decidua × *Larix kaempferi*	European larch × Japanese larch						Arcade et al. 2002
Pinus caribaea × *Pinus elliottii*	Caribbean pine × Slash pine	Shepherd et al. 2006					Shepherd et al. 2003
Pinus elliottii × *Pinus palustris*	Slash pine × Longleaf pine	Shepherd et al. 2006					

Pinus pinaster	Maritime pine	Plomion et al. 1996; Brendel et al. 2002; Chagne et al. 2003					Markussen et al. 2003; Pot et al. 2006
Pinus radiata	Monterey pine	Emebiri et al. 1997, 1998a,b					Kumar et al. 2000; Devey et al. 2004
Pinus sylvestris	Scots pine	Lerceteau et al. 2000	Hurme et al. 1997, 2000	Lind et al. 2007	Hurme et al. 1997		
Pinus taeda	Loblolly pine	Kaya et al. 1999; Chagne et al. 2003; Gwaze et al. 2003; Williams et al. 2007					Weng et al. 2002
Populus davidiana	Shan Yang	Kim et al. 2004					
Populus tementosa	Chinese white poplar	Zhang et al. 2006					Zhang et al. 2006
Populus trichocarpa × *Populus deltoides*	Black cottonwood × Eastern cottonwood	Wu & Stettler 1994; Bradshaw & Stettler 1995; Wu et al. 1997, 1998; Wu 1998; Li et al. 1999; Ferris et al. 2002; Wullschleger et al. 2005; Rae et al. 2006, 2007, 2008	Bradshaw & Stettler 1995; Li et al. 1999; Chen et al. 2002; Frewen et al. 2000	Newcombe & Bradshaw 1996; Newcombe et al. 1996; Jorge et al. 2005; Tagu et al. 2005		Tschaplinski et al. 2006	
Pseudotsuga menziesii	Douglas-fir	Jermstad et al. 2003	Jermstad et al. 2001a		Jermstad et al. 2001a; Wheeler et al. 2005		
Quercus petraea	Sessile oak		Gailing et al. 2005				Saintagne et al. 2004

(*continued*)

Table 6–5 (*continued*)

Forest Trees							
Scientific name	Common name	Growth	Phenology	Disease resistance	Cold hardiness	Drought tolerance	Wood property
Quercus robur	English oak	Scotti-Saintagne et al. 2004a, 2005; Casasoli et al. 2006	Scotti-Saintagne et al. 2004a; Gailing et al. 2005			Parelle et al. 2007; Brendel et al. 2008	Saintagne et al. 2004
Salix dasyclados × *Salix viminalis*	Mao Zhi Liu × Basket willow	Ronnberg-Wastljung et al. 2005; Weih et al. 2006				Ronnberg-Wastljung et al. 2005	
Salix viminalis × *Salix schwerinii*	Basket willow × Common Osier	Tsarouhas et al. 2002, 2003, 2004				Tsarouhas et al. 2004	

Herbaceous Plants					
Scientific name	Common name	Fitness	Floral morphology	Herbivory	Heavy metal tolerance
Aquilegia formosa × *Aquilegia pubescens*	Western columbine × Sierra columbine		Hodges et al. 2002		
Arabidopsis halleri	N/A				Courbot et al. 2007; Willems et al. 2007
Arabidopsis lyrata	Lyre-leaved rock-cress			Heidel et al. 2006	
Iris fulva × *Iris brevicaulis*	Copper iris × Zigzag iris	Martin et al. 2005, 2006	Bouck et al. 2007		
Mimulus	Monkeyflower	Lin 2000; Hall et al. 2006	Lin & Ritland, 1997; Schemske & Bradshaw 1999; Lin 2000; Bleiweiss 2001; Fishman et al. 2002; Hall et al. 2006		

mapping population parent trees that have not resulted from any more than one generation of phenotypic selection from natural populations. The number of studies from herbaceous, natural plant populations is much less extensive (Table 6–5). The complex traits of study in forest-tree QTL mapping studies fall into six broad categories (growth, phenology, disease resistance, cold hardiness, drought, and wood property). All of these traits can be considered "adaptive," although growth and wood property are generally considered "agronomic" and not specifically "adaptive." Early-generation QTL mapping studies in trees often used rather small population sizes (~100), in which the number of QTLs detected was likely underestimated and the size of effects overestimated. Later studies using population sizes of 500 or more probably provide better estimates of QTL number and effect.

QTL mapping studies in forest trees share many of the same approaches and results. Mapping population parent trees are nearly always highly heterozygous and not inbred. Using a highly heterozygous, non-inbred population results in not all QTL loci segregating, and thus being detectable in individual crosses. Nevertheless, a large proportion of the total phenotypic variance for a trait can be accounted for from individual crosses, although the sizes of individual QTL effects are generally small (1–3%) (Wheeler et al. 2005). The QTL approach is rather powerful for identifying the number of QTLs, their chromosomal regions, and the sizes of their effects; however, the resolution of map position is generally quite crude (10–20 cM), so for large genomes lacking reference sequences, the path to positional cloning of QTLs is long, expensive, and not easily justified. Therefore, the genes underlying adaptive-trait QTLs in forest trees remain unknown.

The situation in herbaceous, natural plant QTL mapping is somewhat different (Table 6–5). Here, the traits of interest are often those leading to speciation events such as floral morphology, and thus hybrid crosses are used to maximize QTL segregation. The number of QTLs for such traits is generally quite few, and the sizes of their individual effects are high, justifying positional cloning of such QTLs that will now be greatly facilitated by the genome sequencing *Arabidopsis lyrata, Aquilegia*, and *Mimulus*. Species such as *A. lyrata* and *Boechera stricta* will be good systems for discovering individual genes underlying complex adaptive traits using combined population genetic, QTL mapping, and association approaches.

Candidate-gene association studies in plants

Association studies in natural plant systems are candidate-gene–based due to the lack of reference genome sequences. Studies have been published for four forest-tree species and two herbaceous species (Table 6–6). The studies in *Populus*, *Eucalyptus*, and *A. lyrata* included only one candidate gene each, whereas the *Pinus, Pseudotsuga*, and *Zea mays* ssp. *mays* included many candidate genes each. All species are characterized by a rapid decay of LD, particularly the conifer species (Neale & Savolainen 2004), so the search for associations is challenging, but when an association is found, it is quite likely that the polymorphism is within the gene determining the complex trait (or at least closely linked). Full gene-space candidate-gene association studies are experimentally and economically tractable

Table 6–6. Examples of candidate-gene association analyses in plant species

Species	Common name	Trait	Candidate genes	Reference
Trees				
Eucalyptus nitens	Shining gum	Wood properties	*CCR*	Thumma et al. 2005
Pinus taeda	Loblolly pine	Drought tolerance	*dhn-1, dhn-2, lp3-1, wrky-like, sod-chl*	Gonzalez-Martinez et al. 2008
		Wood properties	*cad, sams-2, comt-2, dhn-2, lp3–3, 4cl, ccr-1, α-tubulin, ccoaomt-1, agp-6, agp-like, c3h-1, c4h-1, c4h-2, cesA3β*	Gonzalez-Martinez et al. 2007
Pseudotsuga menziesii	Douglas-fir	Growth phenology cold-tolerance	*60s RPL31a*, CN639236.1 (guanine nucleotide-binding protein), ES421311.1 (hypothetical protein), Pm_CL783Contig1 (SOUL heme-binding family protein), *4CL1*, *LEA-EMB11*, CN637339.1 (hypothetical protein), CN638489.1 (α-expansin), sSPcDFD040B03103 (MADS-box transcription factor), CN637306.1 (MYB-like transcription factor), *f3h2*, Pm_CL234Contig1 (rab GTPase)	Eckert et al., 2009b
Herbaceous plants				
Arabidopsis lyrata	Lyre-leaved rock-cress	Herbivory	*GL1*	Kivimaki et al. 2007
Zea mays ssp. *parviglumis*	Balsas teosinte	Domestication	*d8, id1, tb1, te1, ts2, zap1, zen1, zfl2, ba1, elm1, ids1, ra1, ra2, su1, tb1, te1, td1, zagl1, zfl1, zfl2, ZmCIR1, ZmGI*	Weber et al. 2007, 2008

to perform with current generation sequencing and SNP genotyping technologies, and a large number of studies in a variety of forest-tree and herbaceous-plant species are now underway.

Tests for signatures of natural selection in plants

Population genetic approaches (i.e., tests of neutrality and outlier analysis) have been applied to large numbers of genes in the model plant *Arabidopsis thaliana* and in the domesticated crop (*Zea mays* ssp. *mays*). In a review by Wright and Gaut (2005), it is reported that as many as 20% of the genes may be under some form of selection, although that number is likely an overestimate. In natural plant populations, there are fewer studies and few genes have been evaluated (Table 6–7). Early resequencing studies in which tests of neutrality were performed included

Table 6–7. Examples of tests of neutrality or outlier analysis in natural plant populations

Species	Common name	No. of genes studied	Marker type	Reference
Trees				
Abies kawakamii	Kawakami fir	1	SNP, microsatellites, cDNA	Shih et al. 2007
Betula pendula	European white birch	2	Microsatellites	Jarvinen et al. 2003
Cathaya argyrophylla	Yin Shan	8	SNP, mitochondrial DNA	Wang & Ge 2006
Cryptomeria japonica	Sugi	7	SNP	Kado et al. 2003
Cunninghamia konishii	China fir	1	SNP	Hwang et al. 2003
Cunninghamia lanceolata	China fir	1	SNP	Hwang et al. 2003
Picea abies	Norway spruce	1, 22	SNP	Guillet-Claude et al. 2004; Heuertz et al. 2006
Picea glauca	White spruce	47	SNP	Namroud et al. 2008
Picea mariana	Black spruce	2	SNP	Guillet-Claude et al. 2004
Pinus lambertiana	Sugar pine	1	SNP	Jermstad et al. 2006
Pinus pinaster	Maritime pine	8	SNP	Pot et al. 2005
Pinus radiata	Monterey pine	8	SNP	Pot et al. 2005
Pinus sylvestris	Scots pine	1, 2, 14	SNP	Dvornyk et al. 2002; Garcia-Gil et al. 2003; Wachowiak et al. 2009
Pinus taeda	Loblolly pine	19, 18	SNP	Brown et al. 2004; Gonzalez-Martinez et al. 2006a
Populus tremula	European aspen	1, 5, 1	SNP	Ingvarsson 2005; Ingvarsson et al. 2006; Garcia & Ingvarsson 2007
Pseudotsuga menziesii	Douglas-fir	18, 121	SNP	Krutovsky & Neale 2005; Eckert et al. 2009a
Quercus petraea	Durmast oak	2	Microsatellites, SCARS, AFLP	Scotti-Saintagne et al. 2004b
Quercus robur	English oak	2	Microsatellites, SCARS, AFLP	Scotti-Saintagne et al. 2004b
Taxodium distichum	Bald cypress	4	SNP	Kado et al. 2006
Herbaceous plants				
Helianthus annuus	Sunflower	9	SNP	Liu & Burke 2006
Hordeum vulgare ssp. *spontaneum*	Barley	1, 9, 18, 877	SNP	Morrell et al. 2003, 2005; Rostoks et al. 2005; Jones et al. 2008
Oryza rufipogon and Oryza nivara	Rice	1, 10	SNP	Wang et al. 2007; Zhu et al. 2007
Persea americana	Avocado	4	SNP	Chen et al. 2008
Solanum ssp.	Tomato	8, 14	SNP	Roselius et al. 2005; Arunyawat et al. 2007

SCARS = sequence characterized amplified regions

one to no more than twenty genes. Based on the small sample of genes, it was not possible to gain an estimate of what proportion of these genomes might be under selection. Recent studies (Eckert et al. 2009a; Song et al. 2009) have reported neutrality tests for nearly 100 or more genes. These studies, combined with the earlier studies, suggest that approximately 10% of the genes may be under selection (Neale 2007). Thus, candidate-gene resequencing and tests of neutrality are efficient approaches toward identifying candidate genes for association studies that might underlie complex adaptive traits in natural plant populations. Furthermore, there is often a functional basis for candidate genes underlying a complex trait (Gonzalez-Martinez et al. 2006b; Eckert et al. 2009b). With the exception of *Populus trichocarpa* and *A. lyrata*, plants from natural populations lack a reference genome sequence to facilitate gene resequencing, although many have fairly rich expressed sequence tag (EST) databases. The newest generation of sequencing technologies makes it experimentally and economically possible to resequence large numbers of genes from natural plant systems.

The outlier approach has been applied to only a couple of natural plant populations to identify candidate genes (Scotti-Saintagne et al. 2004b; Namroud et al. 2008). The oak (Scotti-Saintagne et al. 2004b) and spruce (Namroud et al. 2008) studies identified 12% and 14% outlier loci, respectively. These percentages are consistent with estimates from neutrality testing of the proportion of genes under selection.

CASE STUDY: QTL, ASSOCIATION GENETICS, AND TESTS FOR NATURAL SELECTION IN A NATURAL FOREST-TREE POPULATION

As an animal example is provided in the boxed case study within this chapter, here we provide another example using the forest tree, Douglas-fir, as a case study for how combined population and quantitative genetic approaches can be used to discover the genes underlying a complex adaptive trait in a non-model and non-domesticated plant. Douglas-fir is a long-lived, woody perennial with limited genetic resources; it is not an organism that generally would be thought of as having attributes for easy identification of the genes underlying a complex adaptive trait. We show, however, that the combined population and quantitative genetic approaches we have outlined in this chapter can be applied to an organism such as Douglas-fir and how the knowledge derived can be applied in resource management strategies to help mitigate the impacts of climate change.

The adaptive complex traits of interest were bud phenology and cold-hardiness. Douglas-fir has a broad and ecologically diverse habitat in western North America. There is an extensive literature on the genetics of phenology and cold-hardiness in Douglas-fir based on a common garden approach (Campbell & Sorensen 1979; Aitken & Adams 1996, 1997; Rehfeldt 1997; Anekonda et al. 2000; St. Clair et al. 2005; St. Clair 2006). These studies clearly demonstrate the genetic control (high heritability) and adaptive patterns of variation across complex ecological landscapes. We surmised that phenology and cold-hardiness in Douglas-fir might then be good target complex adaptive traits to apply population and quantitative genetics approaches to finding the underlying genes.

The first step was to apply QTL mapping. A three-generation outbred pedigree was constructed, and the clonally propagated F_2 offspring were planted at two different test-site locations (Jermstad et al. 2001a,b). A restriction fragment length polymorphism (RFLP) linkage map was constructed (Jermstad et al. 1998), and the progeny were evaluated for bud phenology and cold-hardiness. Several QTLs for each of these traits were detected and mapped. Because the size of the segregating population was relatively small, however, it was likely that some QTLs were undetected and the sizes of individual QTL effects were overestimated. The parent trees were then re-mated to develop a much larger (~500) clonally replicated F_2 segregating population. In this experiment, however, the progeny were grown under experimental treatment conditions so that specific environmental cues (winter chill, spring heat sum, photoperiod, and moisture stress treatments) by QTL interactions could be estimated (Jermstad et al. 2003; Fig. 6–2). The goal of this aspect of the experiment was to identify QTLs interacting with specific cues from the environment and thus potentially giving clues as to the specific gene underlying the QTL. These QTL mapping experiments provided the first indications of the number of QTLs affecting bud phenology and cold-hardiness in Douglas-fir and their approximate locations in the genome, but the low-level resolution of their map position provided little indication of the specific genes underlying the QTL. A small number of candidate genes were mapped to the QTL maps, but again the resolution was rather crude (Wheeler et al. 2005).

In the next phase, the population-genomics approach was used to help identify candidate genes for cold-hardiness. In two studies, lists of 18 candidate genes (Krutovsky & Neale 2005) and 121 candidate genes (Eckert et al. 2009a) were developed based primarily on their function in *A. thaliana*. Amplicons from these candidate genes were resequenced in a small ($n = 24$) diversity panel to discover SNPs. The sequence polymorphism database developed from resequencing could then be used to estimate measures of nucleotide diversity and divergence and perform tests of neutrality. From these tests, six genes departed from neutrality and revealed signatures of selective sweeps (Table 6–8; Eckert et al. 2009a). In the next phase, these genes and others were tested for association with bud phenology and cold-hardiness to provide the quantitative genetic line of evidence that the genes underlying adaptive trait QTLs are now known.

An association mapping study was designed to test for association between SNPs in 117 candidate genes, including the 6 genes identified from the population-genomics approach (Table 6–8), and 21 adaptive-trait phenotypes, including bud phenology and cold-hardiness (Eckert et al. 2009b). An association population of 700 open-pollinated families from Douglas-fir trees sampled throughout the states of Washington and Oregon was assembled. Progeny from these families were grown in a randomized common garden, and all 21 phenotypes were evaluated. A maternal breeding value was estimated for each trait and each family. Next, an Illumina GoldenGate genotyping chip was designed that contained 384 SNPs from the 117 candidate genes. All 700 mother trees were genotyped for all 384 SNPs. The phenotype–genotype data set used included 21 traits and 228 high-quality SNP genotypes. A general linear model was used to test for associations between SNPs and the traits measured, and 30 significant associations were found (Eckert et al. 2009b). There were not, however, any

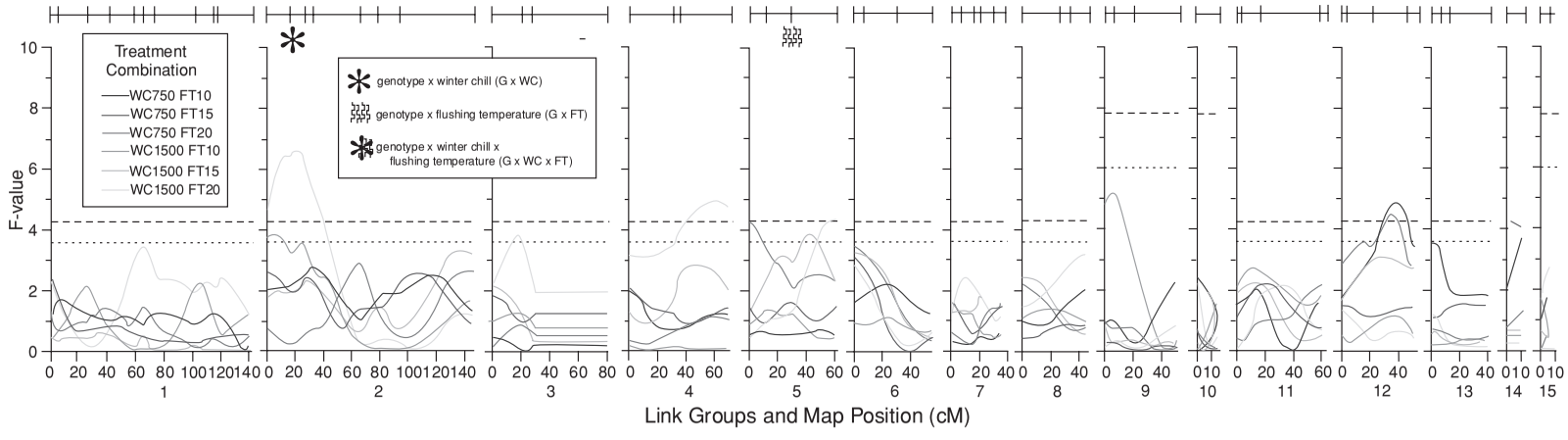

Figure 6–2: Terminal bud flush (TBF_{GI}) was used as a surrogate trait to measure growth initiation in the spring. The overwintering bud is released from dormancy and growth is initiated. Seven QTLs for TBF were detected in the growth initiation experiment (TBF_{GI}). QTLs were found on six linkage groups (LGs 2, 3, 4, 5, 12, and 14) and were detected in five of the six treatment (T) combinations. Only two QTL × T interactions were found, one for winter chill on LG2 and one for flushing temperature on LG5. The interaction detected on LG5 is located at a marker that is intermediate between two QTLs detected by interval mapping (from Jermstad et al. 2003). *See Color Plate VIII.*

Table 6–8. A list of candidate genes putatively affected by directional natural selection (from Eckert et al. [2009a])

Locus	Gene product	Result[a]
Compound DHEW test		
Pm_CL908Contig1	GRAM-containing/ABA-responsive protein	$p_D = .001$, $p_H < .001$, $p_{EW} = .080$
ES420171.1	Cold-regulated plasma membrane protein	$p_D = .009$, $p_H = .050$, $p_{EW} = .035$
ES420250.1	Dehydrin-like protein	$p_D = .072$, $p_H = .083$, $p_{EW} = .042$
CN634517.1	Lumenal-binding protein	$p_D = .034$, $p_H = .148$, $p_{EW} = .076$
Polymorphism-to-divergence		
Pm_CL61Contig1	Cyclosporin A-binding protein	$k = 0.32$
Pm_CL908Contig1	GRAM-containing/ABA-responsive protein	$k = 0.58$
CN638556.1	Transcription regulation protein	$k = 0.41$
Synonymous-to-nonsynonymous divergence		
Pm_CL922Contig1	Thaumatin-like protein	Ka/Ks = 14.48, $\theta_\pi / D_{xy} = 0.087$
CN634677.1	LRR receptor-like protein kinase	Ka/Ks = 10.78, $\theta_\pi / D_{xy} = 0.066$

[a] Results for the *DHEW* test are given as *p* values for each of the component tests (D = Tajima's D; H = Fay and Wu's H; EW = Ewen–Watterson test) comprising the joint test. Values for the EW test are one minus the left-tailed probabilities (cf.). Listed are *p* values for drift within a constant size population. Loci were significant when demographic models included in the simulations are bolded. For polymorphism-to-divergence tests, parameter estimates for a maximum likelihood implementation of the Hudson-Kreitman-Aguadé test are listed. Estimates of k are from a nested model where all three putative targets of selection are allowed to have free parameters. The parameter k specifies the level of elevation ($k > 1$) or reduction ($k < 1$) in diversity relative to divergence. Ka/Ks values were considered extreme when greater than 5.

genes in common between the population genomic approach and the association approach. This study was based on just 121 genes, so that when it was repeated with a large number of genes, one would expect to find many genes in common between approaches. These genes would be those most likely to be underlying complex adaptive traits and be under natural selection in populations of Douglas-fir.

THE GENES OF ADAPTIVE DIFFERENTIATION: UTILITY FOR CONSERVATION AND MANAGEMENT

Although genetics has historically been used to infer relationships among populations and species from "neutral" genetic information, adding information regarding the genetic architecture and genes involved in adaptive phenotypic diversification has great promise for conservation and management of natural, free-living populations. Bonin and colleagues (2007) describe a new index of population adaptation using results from population-genomic approaches and have found that diversity estimates from neutral and adaptive sets of loci are uncorrelated and tell different stories about the standing genetic diversity within and between populations. The idea that neutral and adaptive indices of diversity show different patterns is not new, however, and is an important consideration for the future of conservation genetics (Crandall et al. 2000; Merila & Crnokrak 2001; Reed & Frankham 2003; Kohn et al. 2006; Leinonen et al. 2008). The goal of most conservation programs for wild populations of organisms has been to maintain

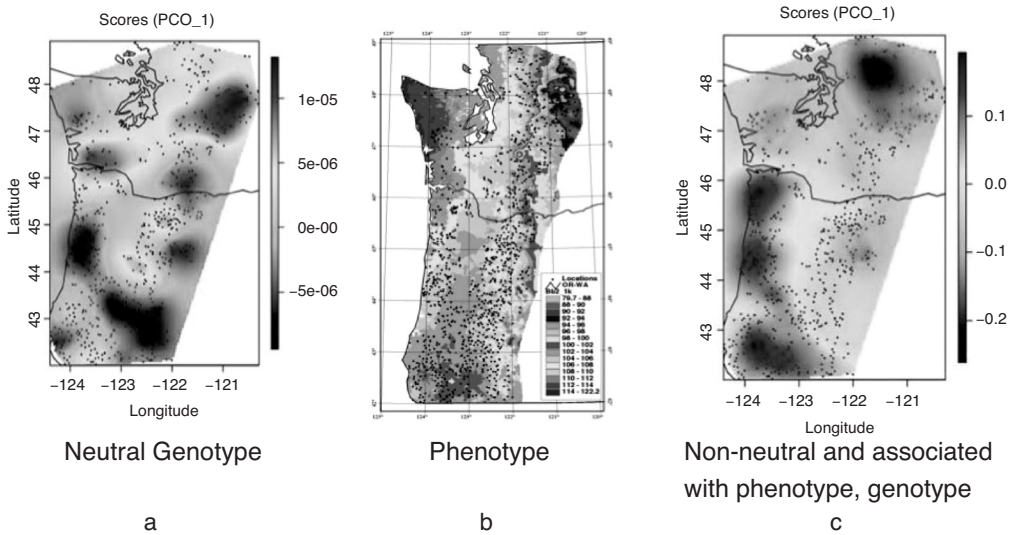

Figure 6–3: Patterns of neutral genetic diversity (a), phenotypic diversity (b), and adaptive genetic diversity (c). *See Color Plate IX*.

genetic diversity, while preserving local adaptations (Moritz 2002; Bonin et al. 2007). In other words, most conservation programs recognize both the phenotypic differences among populations and the demographic processes revealed by population genetic analysis in evaluating long-term population viability and delineating units for conservation (see Moritz 2002 for a review).

One of the key components required for the maintenance of genetic diversity is in obtaining baseline information about the genetic diversity in species and populations of interest so that in the face of anthropogenic impacts and environmental change, the influences of this change on genetic diversity may be monitored (Schwartz et al. 2007; Hoffmann & Willi 2008). Many natural plant and animal populations are threatened by the effects of environmental change. Populations that are currently adapted to a geographic region may no longer be adapted to that location due to changes in temperature, moisture availability, and other environmental factors. It is therefore important to develop detailed and precise descriptions of standing adaptive genetic variation in plant and animal populations so that monitoring activities can be implemented to detect genetic changes in populations. Incorporating genetic information from candidate regions associated with adaptive traits has been historically difficult, as the information has simply not been available for non-model species; however, this trend is changing as studies begin to reveal the genes and shifts in allele frequencies at those genes in response to environmental changes (Hoffmann & Willi 2008). Monitoring the changes in allele frequencies of genes underlying adaptive phenotypes, after being identified, is relatively straightforward. In an example from the Douglas-fir case study earlier in text, the patterns of diversity within non-neutral, phenotype-associated candidate genes show significant similarity to the patterns of phenotypic variation (Fig. 6–3). In contrast, there is little similarity in patterns of variation between neutral genetic variation and phenotypic variation in this system. It can be imagined how land managers might use

geographic information system (GIS)-type applications to lay standing patterns of adaptive genetic variation over predicted environmental patterns (*sensu* Joost et al. 2007, temperature, moisture, etc.) and to develop strategies for assisted migration of genotypes to ensure adaptation in the face of climate change. It is clear that the population and quantitative genomic approaches to understanding adaptive genetic variation in natural plant and animal populations will be of great value in genomically assisted gene-resource conservation and management strategies to mitigate the negative effects of environmental change.

The inclusion of genes underlying adaptive phenotypes will become imperative in conservation genetics, but much work remains on the details of which and how many "adaptive" loci to include in conservation genetic analyses. Hoffman and Willi (2008) review recent theoretical advances in this area and suggest that using loci that explain more than 5% of the phenotypic variation within and among populations will be useful in identifying shifts in allele frequencies in response to environmental change. Just as research on the number of loci and alleles per loci has been important in population genetics using "neutral" loci, the selection of genetic loci that contribute to a significant portion of the phenotypes describing differences among individuals within and across populations and species boundaries will be an active area of ongoing and future research.

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