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Population Genetics and Ecology

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OUTLINE

About 40 years ago, scientists first strongly advocated the integration of population ecology and population genetics into population biology (Singh and Uyenoyama, 2004). Even today these two disciplines are not really integrated, but there is a general appreciation of population genetic concepts in population ecology and vice versa. For example, the new subdiscipline molecular ecology, and many articles in the journal *Molecular Ecology*, use genetic markers and principles to examine both ecological and evolutionary questions. Although some aspects of population genetics have changed quickly in recent years, many of its fundamentals are still important for aspects of ecological study.

GLOSSARY

coalescence. The point at which common ancestry for two alleles at a gene occurs in the past.

effective population size. An ideal population that incorporates such factors as variation in the sex ratio of breeding individuals, the offspring number per individual, and numbers of breeding individuals in different generations.

gene flow. Movement between groups that results in genetic exchange.

genetic bottleneck. A period during which only a few individuals survive and become the only ancestors of the future generations of the population.

genetic drift. Chance changes in allele frequencies that result from small population size.

Hardy-Weinberg principle. After one generation of random mating, single-locus genotype frequencies can be represented as a binomial function of the allele frequencies.

neutral theory. Genetic change is primarily the result of mutation and genetic drift, and different molecular genotypes are neutral with respect to each other.

population. A group of interbreeding individuals that exist together in time and space.

selective sweep. Favorable directional selection that results in a region of low genetic variation closely linked to the selected region.

1. INTRODUCTION

The primary goals of population genetics are to understand the factors determining evolutionary change and stasis and the amount and pattern of genetic variation within and between populations (Hedrick, 2005; Hartl and Clark, 2007). In the 1920s and 1930s, shortly after widespread acceptance of Mendelian genetics, the theoretical basis of population genetics was developed by Ronald A. Fisher, J.B.S. Haldane, and Sewall Wright. Population genetics may be unique among biological sciences because it was first developed as a theoretical discipline by these men before experimental research had a significant impact.

The advent of molecular genetic data of populations in the late 1960s and DNA sequence data in the 1980s revolutionized population genetics and produced many new questions. Population genetics and its evolutionary interpretations provided a fundamental context in which to interpret these new molecular genetic data. Further, population genetic approaches have made fundamental contributions to understanding the role of molecular variation in adaptive differences in morphology, behavior, and physiology. A primary goal in determining the extent and pattern of genetic variation is to document the variation that results in selective differences among individuals, the "stuff of evolution."

The amount and kind of genetic variation in populations are potentially affected by a number of factors, but primarily by selection, inbreeding, genetic drift,

gene flow, mutation, and recombination. These factors may have general or particular effects; for example, genetic drift and inbreeding can be considered to always reduce the amount of variation, and mutation to always increase the amount of variation. Other factors, such as selection and gene flow, may either increase or reduce genetic variation, depending on the particular situation. Combinations of two or more of these factors can generate many different levels and patterns of genetic variation. In 1968, Motoo Kimura introduced the important "neutral theory" of molecular evolution that assumes that genetic variation results from a combination of mutation generating variation and genetic drift eliminating it (Kimura, 1983). This theory is called neutral because allele and genotype differences at a gene are selectively neutral with respect to each other. This theory is consistent with many observations of molecular genetic variation (see below).

To understand the influence of these evolutionary factors, one must first be able to describe and quantify the amount of genetic variation in a population and the pattern of genetic variation among populations. In recent years, new laboratory techniques have made it possible to obtain molecular genetic data in any species, and a number of software packages have become available to estimate the important parameters in population genetics and related topics. In addition, the online Evolution Directory (EvolDir) is a source of information about different molecular techniques, estimation procedures, and other current evolutionary genetic information.

Let us first define the evolutionary or genetic connotation of the term *population*. As a simple ideal, a population is group of interbreeding individuals that exist together in time and space. Often it is assumed that a population is geographically well defined, although this may not always be true. Below we discuss the concept of effective population size, which provides a more explicit definition of population in evolutionary terms.

Many of the theoretical developments in population genetics assume a large, random-mating population that forms the gene pool from which the female and male gametes are drawn. In some real-life situations, such as dense populations of insects or outcrossing plants, this ideal may be nearly correct, but in many natural situations, it is not closely approximated. For example, there may not be random mating, as in self-fertilizing plants, or there may be small or isolated populations as in rare or endangered species. In these cases, modifications of the theoretical ideal must be made.

One of the basic concepts of population genetics is the Hardy-Weinberg principle (often called Hardy-Weinberg equilibrium [HWE]). It states that after one generation of random mating, single-locus genotype frequencies can be represented by a binomial (with two alleles) or multinomial (with multiple alleles) function of the allele frequencies. This principle allows great simplification of the description of a population's genetic content by reducing the number of parameters that must be considered. Furthermore, in the absence of factors that change allele frequency (selection, genetic drift, gene flow, and mutation), and in the continued presence of random mating, the Hardy-Weinberg genotype proportions will not change over time.

2. GENETIC DRIFT AND EFFECTIVE POPULATION SIZE

Since the beginning of population genetics, there has been controversy concerning the importance of chance changes in allele frequencies because of small population size, termed *genetic drift*. Part of this controversy has resulted from the large numbers of individuals observed in many natural populations, large enough to think that chance effects would be small in comparison to the effects of other factors, such as selection and gene flow. However, if the selective effects or amount of gene flow are small relative to genetic drift, then long-term genetic change caused by genetic drift may be important.

Under certain conditions, a finite population may be so small that genetic drift is significant even for loci with sizable selective effects, or when there is gene flow. For example, some populations may be continuously small for relatively long periods of time because of limited resources in the populated area, low tendency or capacity to disperse between suitable habitats, or territoriality among individuals. In addition, some populations may have intermittent small population sizes. Examples of such episodes are the overwintering loss of population numbers in many invertebrates and epidemics that periodically decimate populations of both plants and animals. Such population fluctuations generate genetic bottlenecks, or periods during which only a few individuals survive and become the only ancestors of the future generations of the population.

Small population size is also important when a population grows from a few founder individuals, a phenomenon termed *founder effect*. For example, many island populations appear to have started from a very small number of individuals. If a single female who was fertilized by a single male founds a population, then only four genomes (assuming a diploid organism), two from the female and two from the male, may start a new population. In plants, a whole population may be initiated from a single seed—only two genomes, if

self-fertilization occurs. As a result, populations descended from a small founder group may have low genetic variation or by chance have a high or low frequency of particular alleles.

Another situation in which small population size is of great significance occurs when the population (or species) in question is one of the many threatened or endangered species (Allendorf and Luikart, 2007). For example, all approximately 500 whooping cranes alive today descend from only 20 whooping cranes that were alive in 1920 because they were hunted and their habitat destroyed. All 200,000 northern elephant seals alive today descend from as few as 20 that survived nineteenth-century hunting on Isla Guadalupe, Mexico. Further, all the living individuals of some species are descended from a few founders that were brought into captivity to establish a protected population, such as Przewalski's horses (13 founders), California condors (13 founders), black-footed ferrets (6 founders), Galápagos tortoises from Española Island (15 founders), and Mexican wolves (7 founders).

The population size that is relevant for evolutionary matters, the number of breeding individuals, may be much less than the total number of individuals in an area, the census population size, and is the appropriate measure for many population ecology studies. The size of the breeding population may sometimes be estimated with reasonable accuracy by counting indicators of breeding activity such as nests, egg masses, and colonies in animals or counting the number of flowering individuals in plants. But even the breeding population number may not be indicative of the population size that is appropriate for evolutionary considerations.

For example, factors such as variation in the sex ratio of breeding individuals, the offspring number per individual, and numbers of breeding individuals in different generations may be evolutionarily important. All these factors can influence the genetic contribution to the next generation, and a general estimate of the breeding population size does not necessarily take them into account. As a result, the effective population size, or N_e, a theoretical concept that incorporates variation in these factors and allows general predictions or statements irrespective of the particular forces responsible, is quite useful. In other words, the concept of an ideal population with a given effective size enables us to draw inferences concerning the evolutionary effects of finite population size by providing a mechanism for incorporating factors that result in deviations from the ideal.

The concept of the effective population size makes it possible to consider an ideal population of size N in which all parents have an equal expectation of being the parents of any progeny individual. In other words, the gametes are drawn randomly from all breeding individuals, and the probability of each adult producing a particular gamete equals $1/N$, where N is the number of breeding individuals. A straightforward approach that is often used to tell the impact of various factors on the effective population size is the ratio of the effective population size to breeding (or sometimes census) population size, that is, N_e/N. Sometimes, this ratio is only around 0.1 to 0.25, indicating that the effective population size may be much less than the number of breeding individuals. In general, the effect of genetic drift is a function of the reciprocal of the number of gametes in a population, $1/(2N_e)$, for a diploid population. If N_e is large, then this value is small, and there is little genetic drift influence. Or, if N_e is small, then this value is relatively large, and genetic drift may be important.

3. NEUTRAL THEORY

Neutral theory assumes that selection plays a minor role in determining the maintenance of molecular variants and proposes that different molecular genotypes have almost identical relative fitnesses; that is, they are neutral with respect to each other. The actual definition of selective neutrality depends on whether changes in allele frequency are primarily determined by genetic drift. In a simple example, if s is the selective difference between two alleles at a locus, and if $s < 1/(2N_e)$, the alleles are said to be neutral with respect to each other because the impact of genetic drift is larger than selection. This definition implies that alleles may be effectively neutral in a small population but not in a large population. Neutral theory does not claim that the relatively few allele substitutions responsible for evolutionarily adaptive traits are neutral, but it does suggest that the majority of allele substitutions have no selective advantage over those that they replace.

Kimura also showed that the neutral theory was consistent with a molecular clock; that is, there is a constant rate of substitution over time for molecular variants. To illustrate the mathematical basis of the molecular clock, let us assume that mutation and genetic drift are the determinants of changes in frequencies of molecular variants. Let the mutation rate to a new allele be u so that in a population of size $2N$ there are $2Nu$ new mutants per generation. It can be shown that the probability of chance fixation of a new neutral mutant is $1/(2N)$ (the initial frequency of the new mutant). Therefore, the rate of allele substitution k is the product of the number of new mutants per generation and their probability of fixation, or

$$k = 2Nu\left(\frac{1}{2N}\right) = u.$$

In other words, this elegant prediction from the neutral theory is that the rate of substitution is equal to the mutation rate at the locus and is constant over time. Note that substitution rate is independent of the effective population size, a fact that may initially be counterintuitive. This independence occurs because in a smaller population there are fewer mutants; that is, $2Nu$ is smaller, but the initial frequency of these mutants is higher, which increases the probability of fixation, $1/2N$, by the same magnitude by which the number of mutants is reduced. This simple, elegant mathematical prediction and others from the neutral theory provide the basis for the most important developments in evolutionary biology in the past half-century.

One of the appealing aspects of the neutral theory is that, if it is used as a null hypothesis, then predictions about the magnitude and pattern of genetic variation are possible. Initially, molecular genetic variation was found to be consistent with that predicted from neutrality theory. In recent years, examination of neutral theory predictions in DNA sequences has allowed tests of the cumulative effect of many generations of selection, and a number of examples of selection on molecular variants have been documented (see below).

Traditionally, population genetics examines the impact of various evolutionary factors on the amount and pattern of genetic variation in a population and how these factors influence the future potential for evolutionary change. Generally, evolution is conceived of as a forward process, examining and predicting the future characteristics of a population. However, rapid accumulation of DNA sequence data over the past two decades has changed the orientation of much of population genetics from a prospective one investigating the factors involved in observed evolutionary change to a retrospective one inferring evolutionary events that have occurred in the past. That is, understanding the evolutionary causes that have influenced the DNA sequence variation in a sample of individuals, such as the demographic and mutational history of the ancestors of the sample, has become the focus of much population genetics research.

In a determination of DNA variation in a population, a sample of alleles is examined. Each of these alleles may have a different history, ranging from descending from the same ancestral allele, that is, identical by descent, in the previous generation to descending from the same ancestral allele many generations before. The point at which this common ancestry for two alleles occurs is called coalescence. If one goes back far enough in time in the population, then all alleles in the sample will coalesce into a single common ancestral allele. Research using the coalescent approach is the most dynamic area of theoretical population genetics because it is widely used to analyze DNA sequence data in populations and species.

4. GENE FLOW AND POPULATION STRUCTURE

In most species, populations are often subdivided into smaller units because of geographic, ecological, or behavioral factors. For example, the populations of fish in pools, trees on mountains, and insects on host plants are subdivided because suitable habitat for these species is not continuous. Population subdivision can also result from behavioral factors, such as troop formation in primates, territoriality in birds, and colony formation in social insects.

When a population is subdivided, the amounts of genetic connectedness among the parts of the population can differ. Genetic connection depends primarily on the amount of gene flow, movement between groups that results in genetic exchange that takes place among the subpopulations or subgroups. When the amount of gene flow between groups is high, gene flow has the effect of homogenizing genetic variation over the groups. When gene flow is low, genetic drift, selection, and even mutation in the separate groups may lead to genetic differentiation.

It is sometimes useful to describe the population structure in a particular geographic framework. For example, within a watershed, there may be separated fish or plant groups that have a substantial amount of genetic exchange between them. On a larger scale, there may be genetic exchange between adjacent watersheds but in smaller amounts than between the groups within a watershed. On an even larger scale, there may be populations in quite separated watersheds that presumably have little direct exchange but may share some genetic history, depending on the amount of gene flow among the adjacent groups or occasional long-distance gene flow. This hierarchical representation is useful in describing the overall relationships of populations of an organism and in documenting the spatial pattern of genetic variation. Recently, there has been increasing interest in landscape and geographic approaches to estimating historical and contemporary gene flow. In addition, *phylogeography*, the joint use of phylogenetic techniques and geographic distributions, has been used to understand spatial relationships and distributions of populations within species or closely related species (Avise, 2000).

In general, the subdivision of populations assumes that the various subpopulations are always present. Another view assumes that individual population subdivisions at particular sites may become extinct and then later be recolonized from other subpopulations, resulting in a *metapopulation*. The dynamics of extinction and recolonization can make metapopulations quite different both ecologically and genetically from the traditional concept of a subdivided population.

Gene flow is central to understanding evolutionary potential and mechanisms in several areas of applied population genetics. First, the potential for movement of genes from genetically modified organisms (GMO) into related wild populations—that is, the gene flow of transgenes into natural populations—can be examined using population genetics. Second, the invasive potential of nonnative plants and animals into new areas may be affected by hybridization (gene flow) between nonnative and native organisms as well as adaptive change. Finally, a number of endangered species are composed of only one, or a few, remaining populations with low fitness. Gene flow from other populations of the same species can result in genetic rescue or genetic restoration of these populations by introducing new variation that allows removal of detrimental variation and restoration of adaptive change.

Estimating the amount of gene flow in most situations is rather difficult. Direct estimates of the amount of movement can be obtained in organisms where different individuals can be identified or individual marks are used. Many approaches have been employed to mark individuals differentially, such as toe clipping in rodents, leg banding in birds, coded-wire tags in fish, and radio transponders in many different vertebrates.

However, both movement of individuals and their incorporation into the breeding population are necessary for gene flow. Using highly variable genetic markers, it is now possible to identify parents genetically and thereby determine the spatial movement of gametes between generations without direct movement information of the parents. Or, individuals can be assigned to specific populations using genetic markers, thereby determining whether they are migrants or not.

Indirect measures of gene flow using genetic markers are useful to confirm behavioral or other observations or when these observations are inconclusive or impossible. Most commonly, the number of successfully breeding migrants between groups is measured using techniques to evaluate population structure. Theoretically, assuming finite subpopulations of size N_e and a proportion m migrants into each subpopulation each generation, then

$$F_{ST} \approx \frac{1}{4N_e m + 1}.$$

When $N_e m$ is large, the measure F_{ST} approaches 0, and when $N_e m$ is small, F_{ST} can approach 1. The value of F_{ST} for a group of populations can be estimated using the amount and pattern of molecular genetic variation over subpopulations.

The availability of molecular and DNA sequence data in many organisms provides a database to determine the relationships between populations or species that are not obvious from other traits. It is generally assumed that molecular genetic data better reflect the true relationships between groups than other data, such as morphology or behavior, because molecular data are less influenced by selective effects. Furthermore, differences between relationships generated from molecular data and from other traits provide an opportunity to evaluate the effect of selective effects on other traits.

Maternally inherited mitochrondrial DNA (mtDNA) data have been the workhorse for phylogeographic research because mtDNA does not recombine in most organisms and, as a result, shows a clearer phylogenetic record than many nuclear genes (chloroplast DNA and Y chromosomes are similarly useful). In addition, the effective population size for mtDNA (as well as for chloroplast DNA and Y chromosomes) is only about one-fourth that of nuclear genes so that divergence occurs about four times faster than for nuclear genes. However, this faster rate of divergence and potentially differential gene flow for the two sexes may cause the signal for these uniparentally inherited genes to be different from the phylogenetic pattern for nuclear genes, which constitute a very large proportion of the genome.

5. SELECTION

In the past few years, with the availability of extensive DNA sequence data for a number of organisms (particularly humans), there has been an intensive search for genomic regions exhibiting a signal of adaptive (positive Darwinian) selection. Many of the genomic regions identified have undergone a "selective sweep" because of favorable directional selection, as indicated by low genetic variation in genetic regions closely linked to the selected gene or regions.

An elegant example of a selective sweep is adaptive melanism in the rock pocket mouse of the southwestern United States (Hoekstra et al., 2004). The mouse is generally light-colored and lives on light-colored granite rocks, but it also has melanic forms that live on relatively recent black lava formations in several

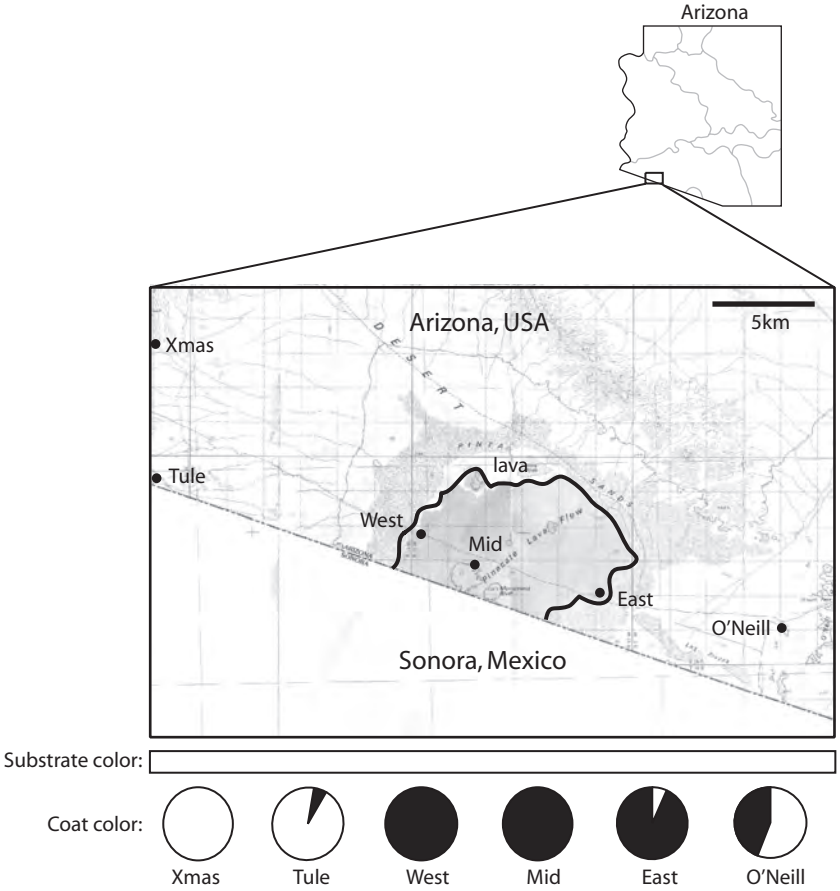

Figure 1. Six sampling sites (three on dark volcanic rock and three on light-colored substrate) and coat color frequencies (in pie diagrams) in rock pocket mice across a transect in the Sonoran desert. (From Hoekstra et al., 2004)

restricted sites. Figure 1 shows the frequencies of the normal recessive and dominant melanic forms from a 35-km transect in southwestern Arizona. Here the frequency of melanics is highly concordant with substrate color, that is, high frequencies of melanics in the center of this transect that has approximately 10 km of black lava and lower frequencies of melanics on the light-colored substrate sites at either end of the transect.

Investigation of molecular variation in the *Mc1r* gene, which is known to have variants that produce dark-colored house mice, was found to correlate nearly completely with the light and melanic phenotypes. The melanic and normal alleles were found to differ by four amino acids, and the nucleotide diversity for the melanic alleles was 1/20 that for light alleles. The lower variation among the melanic alleles is consistent with the expected pattern if selection has recently increased its frequency by a selective sweep in the area of black lava.

Some of best-documented examples of adaptive selection are those resulting from recent human changes in the environment (Hedrick, 2006), such as development of genetic resistance in insect pests to chemicals used to control them or genetic resistance in pathogens to antibiotics. The genetic basis of pesticide resistance may be the result of many genes, mutants at a single or a few genes, or expansion of gene families. Because the molecular basis of many of these adaptive changes is known, detailed genetic and evolutionary understanding is possible. For example, resistance to some insecticides among mosquitoes that are vectors for diseases such as malaria (*Anopheles gambiae*) and West Nile virus (*Culex pipiens*) is the result of a single amino-acid

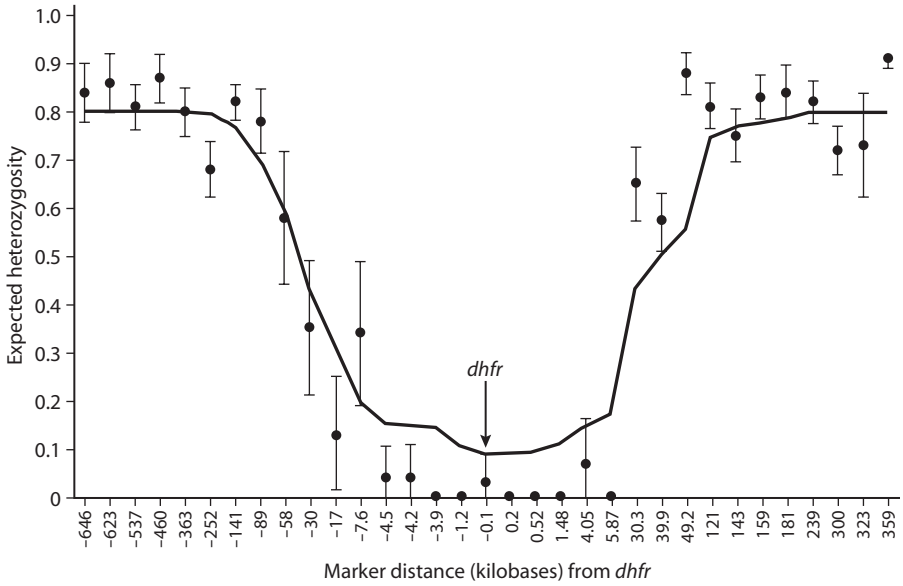

Figure 2. The observed (solid circles) and expected (lines) heterozygosity around the *dhfr* gene in the malaria parasite *Plasmodium falciparum*, which provides resistance to the antimalarial drug pyrimethamine. (From Nair et al., 2003)

substitution. In *C. pipiens*, a single nucleotide change, GGC (glycine) to AGC (serine) at codon 119 in the gene for the enzyme acetylcholinesterase (*ace*-1) results in insensitivity to organophosphates. A complete lack of variation within samples among resistant variants of this gene suggests that they have originated and spread quite recently.

Another set of examples of adaptive selection include those resulting from the development of host resistance to pathogens. For example, malaria kills more than one million children each year in Africa alone and is the strongest selective pressure in recent human history. As a result, selective protection from malaria by sickle cell, thalassemia, G6PD, Duffy, and many other genetic variants in the human host provide some of the clearest examples of adaptive variation and diversifying selection for pathogen resistance (Kwiatkowski, 2005). Genomic studies have demonstrated that selection for malarial resistance is strong, up to 10%, and that variants conferring resistance to malaria are recent, generally less than 5000 years old, consistent with the proposed timing of malaria as an important human disease. Often the resistant variants are in different populations, probably mainly in part because of their recent independent mutation origin.

Efforts to control the malaria parasite using antimalarial drugs have resulted in widespread genetic resistance to these drugs. For example, pyrimethamine is an inexpensive antimalarial drug used in countries where there is resistance in the malarial parasite to the widely used drug chloroquine. Pyrimethamine was introduced to the area along the Thailand-Myanmar border in the mid-1970s, and resistance spread to fixation in approximately 6 years. Resistance is the result of point mutations at the active site of the enzyme encoded by the gene *dhfr* on chromosome 4. Examination of genetic variation at genes near *dhfr* as shown in figure 2 showed remarkable reduced heterozygosity near *dhfr* and normal variation further away (Nair et al., 2003). This pattern of variation is consistent with a selective sweep, and the theoretical pattern expected from a selective sweep is shown by the curve in figure 2.

The major histocompatibility complex (MHC) genes are part of the immune system in vertebrates, and differential selection through resistance to pathogens is widely thought to be the basis of their high genetic variation (Garrigan and Hedrick, 2003). Variation in the genes of the human MHC, known as *HLA* genes, has been the subject of intensive study for many years because of their role in determining acceptance or rejection of transplanted organs, many autoimmune diseases, and recognition of pathogens. High *HLA* variation allows recognition of more pathogens, consistent with the fact that *HLA-B* is the most variable gene in the human genome. In recent years, there has been extensive research examining *R* (disease resistant) genes in plants, a system with similarities to MHC.

6. FUTURE DIRECTIONS

Because of the widespread availability of DNA sequence data in many organisms, the future application of population genetic data and principles in ecology appears almost unlimited. Many basic ecological questions, such as how many individuals there are in a population, what their relationships are, or whether they are immigrants, may be definitively answered in future years using genetic techniques. Such precise descriptions may then provide data to understand the evolutionary and ecological factors influencing population dynamics and distributions.

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