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The genetic basis of adaptation: lessons from concealing coloration in pocket mice

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Abstract

Recent studies on the genetics of adaptive coat-color variation in pocket mice (*Chaetodipus intermedius*) are reviewed in the context of several on-going debates about the genetics of adaptation. Association mapping with candidate genes was used to identify mutations responsible for melanism in four different populations of *C. intermedius*. Here, I review four main results (i) a single gene, the melanocortin-1-receptor (*Mc1r*), appears to be responsible for most of the phenotypic variation in color in one population, the Pinacate site; (ii) four or fewer nucleotide changes at *Mc1r* appear to be responsible for the difference in receptor function; (iii) studies of migration-selection balance suggest that the selection coefficient associated with the dark *Mc1r* allele at the Pinacate site is large; and (iv) different (unknown) genes underlie the evolution of melanism on three other lava flows. These findings are discussed in light of the evolution of convergent phenotypes, the average size of phenotypic effects underlying adaptation, the evolution of dominance, and the distinction between adaptations caused by changes in gene dosage versus gene structure.

Introduction

More than a century after the publication of 'The Origin of Species' many questions about the genetics of adaptation remain unanswered. Darwin (1859) provided a mechanism for evolution, but he was unaware of Mendel, and thus early evolutionary theory was developed without an accurate understanding of the nature of inheritance. The integration of Mendelian inheritance with evolutionary theory was provided by the work of Haldane, Fisher, and Wright, who, among many other things, developed the first models of the dynamics of allele frequency change under various forms of selection (Fisher, 1930; Wright, 1931; Haldane, 1932). In these models, fitness is typically summarized by a single parameter, the selection coefficient, which is usually associated with a particular allele at a single locus. Early empirical studies of adaptation proceeded somewhat independently of the theoretical studies of Fisher, Wright and Haldane. Empiricists such as Dobzhansky (1937, 1970), Dice (1940), Mayr (1942, 1963), Lack (1947), Stebbins (1950) and others began to describe geographic and temporal patterns of phenotypic variation, and many of these patterns provided convincing, though indirect, evidence for selection.

Natural selection acts on the phenotype, but it is the genotype that is passed from one generation to the next. Nonetheless, even today, relatively few studies have been able to make links between genotype and phenotype for traits under selection. To a considerable extent, theoretical studies (often dealing mostly with genotypes) and empirical studies (often dealing mainly with phenotypes) have remained divorced from each other. In principle, finding the genes underlying adaptation might allow us to bring these two approaches together; that is, to study the ecology of adaptation

in the context of explicit population genetic models.

Some of the best examples of the genetic basis of phenotypic responses to selection involve anthropogenic influences, either intentionally through artificial selection, or accidentally through human-induced changes to the environment. It is well known that the first chapter of The Origin of Species (Darwin, 1859) describes extensive changes in phenotype caused by selective breeding. There is now an enormous literature on both plant and animal breeding, and in some cases, the specific genes underlying response to artificial selection have been identified (e.g., Doebley, Stec & Hubbard, 1997; Wang et al., 1999; Newton et al., 2000). Examples of responses to human disturbance include insecticide, herbicide, and drug resistance (Palumbi, 2001; Reznick & Ghalambor, 2001), and in many cases, the genes underlying theses traits have also been identified (e.g., Fidock et al., 2000; Raymond et al., 2001; Walsh, 2000; Cowen, Anderson & Kohn, 2002; Daborn et al., 2002; Wootton et al., 2002; Hughes, 2003). One potential limitation of both kinds of studies for developing a more general understanding of the genetic basis of adaptation is that selection caused by anthropogenic influence is likely to be unusually strong (Darwin, 1859; Reznick & Ghalambor, 2001). Ideally we would like to be able to make links between genotype and phenotype for fitness-related traits in a more natural setting.

Many general questions about the genetics of adaptation remain, and in principle, might be answered by identifying the genes underlying adaptive phenotypes. For example, do adaptations result from the fixation of many mutations individually of small effect (Fisher, 1932), or do they involve single mutations of large effect, as documented for insecticide resistance (e.g. Daborn et al., 2002)? Are most adaptive mutants dominant as suggested by Haldane (1924), and do they correspond to gain-of-function mutations at the molecular level (Wright, 1934)? What kinds of molecular changes result in adaptation; are most adaptations the result of changes in protein structure or changes in gene regulation (Britten & Davidson, 1969)? How common are pleiotropy and epistasis? Do epistatic interactions typically involve other mutations in the same gene or mutations in different genes (Kondrashov, Sunyaev & Kondrashov, 2002)? With the ultimate goal of addressing these and related questions, we have taken a candidate-gene approach to understand the genetic basis of adaptive melanism in the rock pocket mouse, *Chaetodipus intermedius*. While some of these questions can be addressed without identifying the specific mutations underlying a trait, others cannot. Using a candidate-gene approach also has some serious limitations, as discussed below. First, I describe the relevant natural history of pocket mice, including variation in pigmentation. Second, I describe the genetics and biochemistry of mammalian pigmentation and the power and limitations of a candidate-gene approach in this system. Finally, I describe some of our chief findings and their implications for addressing the questions above.

Pigmentation variation in rock pocket mice

The rock pocket mouse, *Chaetodipus intermedius*, is a small rodent that inhabits rocky areas and desert scrub at low elevations principally in the Sonoran and Chihuahuan deserts. Its range includes southern Arizona, southern New Mexico, western Texas, and adjacent areas in northern Mexico. Pocket mice are in the family Heteromyidae, a New World family of rodents that includes six genera (*Chaetodipus*, *Perognathus*, *Dipodomys*, *Microdipodops*, *Liomys*, and *Heteromys*) and has its center of diversification in xeric habitats of Central and North America. Heteromyid rodents are distantly related to murid rodents, such as laboratory mice (*Mus domesticus*). Like many species of heteromyids, rock pocket mice are well adapted for deserts: they are strictly nocturnal and remain in underground burrows during the heat of the day. Pocket mice are so named because of external cheek pouches which are used to carry seeds during bouts of foraging. Pocket mice can subsist entirely on a dry diet and do not require free water. *C. intermedius* is restricted to rocky habitats, and is broadly sympatric with *C. penicillatus*, its sister species, which is found in more sandy habitats.

In most parts of its range, *C. intermedius* has a light, sandy-colored dorsal pelage and lives on light-colored rocks. In several different regions throughout its range, however, *C. intermedius* is found on lava flows which are typically dark in color. The mice on these lava flows typically have a melanic dorsal pelage. Examples of typical habitat