Adaptation from Leaps in the Dark

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Although many adaptations occur by selection of beneficial alleles transformed from neutral or deleterious standing variation, new identical mutant alleles that arise as premeiotic clusters have an increased probability of fixation that can rise to the levels that are similar to the fixation of standing variation. Hence, the evidence is still out on the proportion of adaptations that use preexisting variation and new mutations.

Key words: adaptation, fixations, mutation, standing genetic variation

As part of a discussion of the role of new mutations and standing genetic variation on the adaptation of populations to new environments by selection, Barrett and Schluter (2007) concluded “Compared with new mutations, adaptation from standing genetic variation is likely to lead to faster evolution, the fixation of more alleles of small effects and the spread of more recessive alleles.” This conclusion was based mainly on the assumption that beneficial alleles transformed from neutral, or deleterious, standing variation as a response to changes in the environment will initially be at a higher frequency than new mutations, leading to a considerable advantage in the speed and probability of fixation of preexisting variation over single new mutant alleles (also see Hermisson and Pennings 2005). We believe that there is a common genetic reason why this assumed disparity in frequencies is overstated—new identical mutant alleles often arise as premeiotic clusters (germinal mosaic) within individuals in one place and at the same time, giving these clusters an increased probability of fixation above the assumed single variants (see Figure 1).

Barrett and Schluter (2007) assumed that all new mutant alleles arise as single events. They even define standing genetic variation as the presence of more than one allele at a locus in a population. Mutant alleles, however, do not always arise as single events. Clusters of identical mutant alleles have been observed in all tested higher organisms and natural populations and occur for all types of genetic damage (Hall 1988; Woodruff and Thompson 1992; Drost and Lee 1995; Woodruff et al. 1996; Huai and Woodruff 1997; Selby 1998; Thompson et al. 1998; Woodruff et al. 2004; Woodruff and Thompson 2005; Fischer et al. 2006). For example, about 20–50% of mutations in Drosophila melanogaster occur in clusters (Mason et al. 1985; Woodruff and Thompson 1992; Yang et al. 2001). If a mutation occurs during embryonic development before germ line differentiation, a large proportion of the gametes can theoretically carry the new mutant allele (Figure 1). This prediction is supported by the finding that clusters are not always small in size. For example, in humans where progeny size is not large, there are reports of 4 mutants out of 7 (4/7), 4/4, 4/4, 4/4, and 6/6 for a variety of genetic disorders and up to 29% of sperm from an individual with a new mutation (references in Thompson et al. 1998). In D. melanogaster, 68 identical mutant alleles have been recovered out of 72 total progeny, in mice 166 out of 297, and in guinea pigs 79 out of 228 (Wright and Eaton 1926; Russell LB and Russell WL 1996; Woodruff et al. 1996; Thompson et al. 1998).
Figure 1. Mutations occurring at meiosis give rise to a single mutant allele, whereas mutations occurring before meiosis give rise to a premeiotic cluster of mutant alleles. Modified with permission from Woodruff and Thompson (2005).

Large premeiotic clusters of new mutant alleles have also been recovered from nature; for example, clusters of mutation have been observed in the progeny of olive ridley sea turtles (a cluster of 9 out of 140 total progeny; Hoekert et al. 2002), green turtles (2/3 and 3/6; Fitzsimmons 1998), dollar sunfish (11/45; Mackiewicz et al. 2002), pink salmon (9/50 and 4/48; Steinberg et al. 2002), pipefish (5/13, 2/33, 3/42, 2/59, and 2/9; Jones et al. 1999; Jones and Avise 2001), knobbed whelks (19/503; Walker et al. 2007), lizards (8/11; Porter and Sites 1987), and mountain gorillas (2/5; Nsubuga et al. 2007).

Extensive theoretical analysis has confirmed the significant impact that such clusters can have on a population. These premeiotic clusters increase the probability and decrease the time of fixation of new mutant alleles, reduce the cost of natural selection, increase the probability of reproductive isolation due to new mutant alleles, explain at least part of the overdispersed molecular clock, and alter the fundamental theorem of neutral evolution (Woodruff et al. 1996; Huai and Woodruff 1997, 1998; Woodruff and Thompson 2002; Woodruff et al. 2004; Woodruff and Thompson 2005). Because of their potential effect on the gene pool when they occur, a cluster of mutant alleles cannot be ignored or be counted as a single mutation. All members of a cluster should be counted in the determination of mutation rates (Auerbach 1962; Muller et al. 1963; Drost and Lee 1995; Drake et al. 1998; Neel 1998; Selby 1998; Thompson et al. 1998; Fu and Huai 2003; Gong et al. 2005).

For new advantageous mutant alleles, which are additive (h, the dominance coefficient, is ½), s is the selection coefficient, N is the population size, Nc is the effective population size, Ne = N, and the frequency (p) of a new mutant allele is 1/2N, the probability of fixation of a single beneficial mutant allele is (Rice 2004; Hedrick 2005)

\[ 1 - e^{-4N_{e}hp} = 1 - e^{-4N_{e}(1/2)(1/2N)} = 1 - e^{-2Ns} \]

The probability of fixation of a new beneficial mutant that arises in a cluster of size c, with a frequency of c/2N, is

\[ 1 - e^{-4N_{e}hc} = 1 - e^{-4N_{e}(1/2)c/(2N)} = 1 - e^{-Ns} \]

Note that if the population size is large, Nc = N and s is small, the probability of fixation of a single mutant allele becomes s (2s if h = 1), as suggested by Haldane (1927), whereas the probability of fixation of mutant alleles that arise in clusters of size c is cs (2cs if h = 1). As an example, if s is 0.001 and Nc = N = 10 000, the probability of fixation for a single mutant is 0.001, whereas the probability of fixation of a cluster of 2 is 0.002, and a cluster of 6 is 0.006, giving an increase of probability of fixation over singles equal to the cluster size.

Comparisons of the role of standing genetic variation and new single mutations on adaptive evolution are shown in figure 1 of Barrett and Schluter (2007) and figure 1 of Hermisson and Pennings (2005). These figures show that standing genetic variation is at an advantage over single new mutations. This is not the case, however, if premeiotic clusters of new mutation occur instead of just single mutant alleles. For example, if Nc = N = 25 000, as they assumed,

Figure 2. Probability of fixation of a polymorphic allele (standing genetic variation) that changes from neutral to advantageous compared with that of a single new advantageous mutant allele and premeiotic clusters of new advantageous mutant alleles.
and $s = 0.2$, it would take a cluster of size 10 to give about the same probability of fixation for new mutations versus the probability of fixation that depends on standing genetic variation. See Figure 2 for a comparison of the fixation probabilities of standing variation and clusters. With premeiotic clusters, the probability of fixation of new mutations can rise to levels that are similar to the fixation of transformed standing genetic variation.

Many adaptations do occur by selection on preexisting variation, although there are arguments for the importance of other forces in evolution, including new mutations, recombination, and genetic drift (Kimura 1983; Mani and Clarke 1990; Peck 1994; Li 1997; Gessler and Xu 1998; Orr and Betancourt 2001; Hoffman and McKenzie 2005; Orr 2005; Gillespie 2006; Stoltzfus 2006; Desai and Fisher 2007; Lynch 2007; Nei 2007). We believe, however, that we should not rush to throw out the new mutation babies with the nonadaptive bath water. The evidence is still out on the proportion of adaptations that use standing genetic variation and those that depend on new mutations.

In 1921, at the Second International Congress on Eugenics, R. A. Fisher gave a talk on Darwinian Evolution of Mutations, where he said: “For mutation is necessarily a leap in the dark: the chances of failure are far greater than those of success, especially when the effect of mutation is large” (Fisher 1922). Maybe, Fisher should have discussed mutations not as a leap but as leaps in the dark.

References


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