Letter to the Editor

How Common Are Overdominant Mutations?

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RECENTLY, Peters et al. (2003) reported that hybrids between EMS-mutagenized lines of Caenorhabditis elegans and the ancestral line in some cases had higher productivity and relative fitness than either parental line. They interpreted this as evidence for overdominance (heterozygote superiority) of EMS-induced mutations. A number of other authors have made claims for overdominance of induced or spontaneous mutations (see Peters et al. 2003 for references). For example, using EMS-treated lines in Drosophila melanogaster, Mukai (1970) observed a negative correlation between heterozygous and homozygous viability among the lines with relatively high homozygous viability, which he interpreted as evidence for overdominance.

If overdominant mutations are as common as these studies seem to suggest, then polymorphisms maintained by heterozygote superiority should be widespread. In spite of considerable effort, however, such polymorphisms have been documented in only a handful of cases. In addition, evidence from Drosophila is inconsistent with the view that a large fraction of genetic variation in life-history traits is maintained by heterozygote superiority (Charlesworth and Hughes 1999). This suggests that other explanations for the apparent overdominance of new mutations should be sought.

In this note I show that results like those of Peters et al. (2003) and Mukai (1970) can be explained if deleterious alleles are uniformly partially recessive, with a small fraction of mutations being beneficial under both heterozygous and homozygous conditions. Under these assumptions, apparent overdominance can readily result from the combined effects of the deleterious and beneficial mutations.

To illustrate this point, I consider a simple model in which all deleterious alleles reduce fitness by $hs$ and $s$ under heterozygous and homozygous conditions, respectively. Most mutations are from the beneficial allele to the deleterious one, but a few are from deleterious to beneficial. The beneficial mutations can be reversals of deleterious mutations that happened to be present in the original line or can be totally new mutations (e.g., mutations that compensate for the fixed deleterious mutations). I further assume that $h < 0.5$. A consequence of these assumptions is that beneficial mutations have higher dominance $(1 - h)$ than do deleterious ones $(h)$. This stems from the simple and arguably reasonable assumption that deleterious alleles are all partially recessive to the same degree.

With these assumptions, it is easy to derive the conditions under which a hybrid between a mutant line and the control will have higher fitness than either parent. If control fitness is $w_c$, the fitness of a mutant line with $b$ beneficial and $d$ deleterious mutations will be $w_b + bs - ds$, and the fitness of the hybrids will be $w_b + b(1 - h)s - dh$. The condition for hybrid fitness to exceed $w_c$ is simply $p = b/(b + d) > h$, where $p$ is the proportion of mutations that are beneficial. The condition for hybrid fitness to be greater than that of the homozygous mutant line is simply $1 - p > h$. If deleterious alleles are nearly or completely recessive, both conditions can be satisfied even when a line has many more deleterious than beneficial mutations. Contrary to the suggestion of Peters et al. (2003, p. 596), “spurious” overdominance does not require that a large proportion of mutations are beneficial.

The above assumptions can even lead to a negative correlation between heterozygous and homozygous viabilities, as observed by Mukai (1970). The key requirement is that the variance in the number of mutations per line is considerably greater than expected if mutations are distributed among lines independently. Such a greater-than-Poisson variance can generate a positive correlation between the numbers of beneficial and deleterious mutations per line. Lines with relatively few mutations will have heterozygous and homozygous viability near that of the control. As the number of mutations increases, average homozygous viability will decrease, because most mutations are deleterious, but average heterozygous viability may increase, due to the increasing number of partially dominant beneficial mutations.

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To examine the conditions under which the correlation between heterozygous and homozygous viability is negative, let the number of mutations per line, \( n \), have mean \( \mu_n \) and variance \( \sigma_n^2 \). I assume each mutation has independent probability \( p \) of being beneficial, regardless of the number of mutations per line. The covariance between heterozygous and homozygous viabilities is

\[
\text{COV}[w_i + b(1 - h)s - dhs, w_i + b(1 - h)s + ds] = s^2 \text{COV}[bh + d - b, d - b] = s^2[\sigma_h^2 + (1 - h)\sigma_h^2 - \sigma_d^2],
\]

where \( \sigma_h^2 \) and \( \sigma_d^2 \) are the variances in the number of deleterious and beneficial mutations, respectively, and \( \sigma_d \) is their covariance. These variances and covariance can be evaluated by conditioning on the number of mutations per line, \( n \). For example, \( \sigma_h^2 = E(b^2) - \mu_n^2 \), where

\[
E(b^2) = \sum_{i=0}^{\infty} E(b^2|n = i)P(n = i) = \sum_{i=0}^{\infty} [i^2p(1 - p) + \mu_n^2]P(n = i) = \mu_n^2p(1 - p) + \mu_n^2 + \mu_n^2 = \mu_n^2 + \mu_n^2.
\]

Therefore \( n \) is the proportion of beneficial mutations. Applying the same reasoning to \( \sigma_d^2 \) and \( \sigma_d \) and substituting the results into (1) gives, after simplification,

\[
\text{COV}(het, hom) = s^2[(h - p)(1 - 2\theta) + 2\mu_n(1 - p)] = \theta\sigma_h^2 + 2\mu_n(1 - p) - \theta\sigma_d^2.
\]

It is convenient to define \( \theta = \sigma_n^2/\mu_n \) (with a Poisson distribution, \( \theta = 1 \)). Using this definition, (2) will be negative when

\[
(p - \theta)(1 - 2\theta)p > 2\mu_p(1 - p).
\]

Assuming \( p < 0.5 \), \( p \) must be greater than \( h \) for (3) to be satisfied, and \( \theta \) must be greater than 2. Figure 1 shows minimum \( \theta \) for (3) to be satisfied as a function of \( p \) for various values of \( h \).

It is necessary to invoke overdominance of individual mutations to explain other heterosis in crosses involving individual mutagenized lines (Peters et al. 2003) or a negative correlation between heterozygous and homozygous viabilities (Mukai 1970). Barring experimental artifacts such as stock contamination, which might explain Mukai and Yamazaki’s (1968) evidence for spontaneous overdominant mutations (Fry 2004), it is nonetheless necessary to postulate that a small but nontrivial fraction of mutations have beneficial effects. Determining whether such mutations are truly overdominant or simply partially dominant will require isolating the effects of individual mutations. One way this could be done is by inbreeding from the F2 of crosses between mutagenized and control lines. Under the dominance hypothesis advanced here, but not under the overdominance hypothesis, it should be possible to recover homozygous lines with higher fitness than that of the controls.

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**LITERATURE CITED**


