Neutrality or selection?

In examining a large sample of parent–offspring data from two human major histocompatibility complex loci, HLA-A and HLA-B, from South Amerindians (F. L. Black and P. W. Hedrick, unpublished results), I have discovered a unique bi-allelic model. In this model there are no changes in allelic frequency for any given initial frequency — a neutral equilibrium — but there is a minimum mean fitness and a maximum excess of heterozygotes over Hardy–Weinberg expectations for equal allelic frequencies.

For all types of mating in the sample (see Table 1) that can produce homozygotes, except where the mother is a homozygote and the father is a heterozygote, there is a significant excess of heterozygotes over expected mendelian proportions, with a large (0.46) and statistically significant selection coefficient (s) against homozygotes[1]. These results are suggestive of major histocompatibility complex (MHC) involvement in maternal–fetal interactions where homozygous offspring are selected against when carried by heterozygous mothers.

This selection is described by the bi-allelic model below, where alleles A_1 and A_2 have frequencies of p and q and genotypes A_1A_1, A_1A_2, and A_2A_2 have frequencies of P, H and Q. Note that Hardy–Weinberg proportions are not assumed and that only homozygous progeny from heterozygous mothers are selected against. The mean fitness is $\bar{w} = 1 - sH/2$ and the expected change in the frequency of A_1 is:

$$\Delta q = \frac{q(q - sH/2) + pq - q\bar{w}}{\bar{w}} = 0.$$

Quite surprisingly, there is no change in allelic frequency for any value of q (Fig. 1), just as for the neutrality model, the basis of molecular evolution theory, in which all genotypes have the same fitness.

The equilibrium frequency of heterozygotes is calculated by letting $H_e = H$ so that:

$$H_e = \frac{2pq}{(1 - sH_e/2)} = \frac{1 - (1 - 4spq)^{1/2}}{s}$$

The mean fitness at equilibrium is $\bar{w} = 1 - sH_e/2$. The equilibrium values of heterozygosity and mean fitness are reached quickly from any starting genotypic frequencies.

The mean fitness is a function of allelic frequencies with a minimum at $p = q$ and a maximum when $q = 0$ or 1 (Fig. 1), a pattern reminiscent of selection against heterozygotes[2]. The fixation index $F = 1 - (H_e/2pq)$ is negative (Fig. 1), reminiscent of selection favouring hetero-

zygotes[2]. The maximum excess of heterozygotes over Hardy–Weinberg proportions (the most negative F value) occurs when the allelic frequencies are equal. For example, when the allelic frequencies are equal and $s = 0.5$, then $\bar{w} = 0.854$ and $F = -0.172$.

Heterozygous females have lower fitness than homozygous females because of the lowered average fitness of their offspring. However, they appear to compensate precisely for this by the relatively higher fitness of offspring that are exactly like themselves (heterozygotes), thus explaining the neutrality equilibrium. The relatively higher fitness of their heterozygous offspring results in an overall excess of heterozygous offspring.

However, given two alleles in neutral equilibrium and the generation of a third allele by mutation, this new allele has a selective advantage. In other words, for situations with more than two alleles, such as most MHC genes, this model predicts that selection will maintain a stable polymorphism for multiple alleles.

Figure 1 From top to bottom, the change in allelic frequency (Δq), the mean fitness ($\bar{w}$) and the excess of heterozygotes ($-F$) as a function of allelic frequency for the selection model when $s = 0.5$.

This bi-allelic selection model has no effect on the dynamics of genetic change, but when the two alleles have equal frequency the model results in a minimum fitness and a maximum excess of heterozygotes. This is, to my knowledge, the first description of a selection model with these unique properties.

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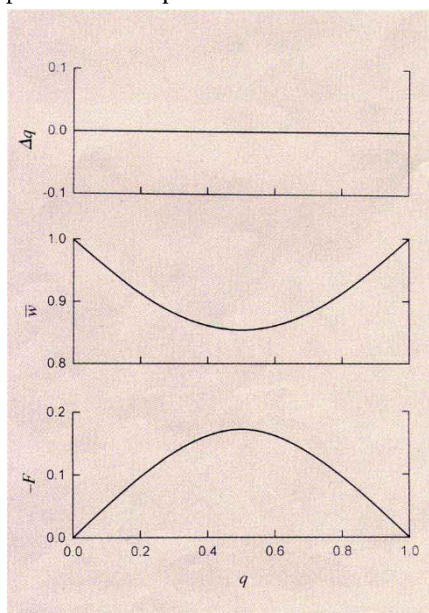*e-mail: hedrick@hedricklab.la.asu.edu*

1. Haldane, J. B. S. *J. Genet.* **54**, 294–296 (1956).
2. Hedrick, P. W. *Genetics of Populations* (Jones & Bartlett, Boston, 1985).

DNA answers the call of pipistrelle bat species

Groups of organisms that have been described as a single taxonomic unit on the basis of quantitative characters are increasingly proving to require more complex classification, when their evolutionary history is studied with molecular markers[1]. Here we report an analysis of mitochondrial DNA sequences from the two echolocating types[2] of Europe's most abundant and well-studied bat, the pipistrelle[3] (*Pipistrellus pipistrellus*). We describe genetic divergence that supports its reclassification as two different species.

Species-specific acoustic signals are especially important in nocturnal animals because of constraints on visual communication in the dark. Species can therefore often be identified by differences in their calls or other acoustic signals[4,5] when morphology and behaviour are poor discriminative tools[6]. A bimodal distribution of echolocation call frequencies of the pipistrelle indicates that there may be a previously unrecognized taxonomic division[2].

Pipistrelles emit echolocation calls with the frequency of most energy close to either 45 or 55 kHz, yet the two phonic types are

Table 1 Selection model

| Parents | | Progeny | | |
Female × Male	Frequency	A_1A_1	A_1A_2	A_2A_2
$A_1A_1 \times A_1A_1$	P^2	1	–	–
$A_1A_1 \times A_1A_2$	PH	1	1	–
$A_1A_1 \times A_2A_2$	PQ	–	1	–
$A_1A_2 \times A_1A_1$	PH	$1 - s$	1	–
$A_1A_2 \times A_1A_2$	H^2	$1 - s$	1	$1 - s$
$A_1A_2 \times A_2A_2$	HQ	–	1	$1 - s$
$A_2A_2 \times A_1A_1$	PQ	–	1	–
$A_2A_2 \times A_1A_2$	HQ	–	1	1
$A_2A_2 \times A_2A_2$	Q^2	–	–	1
		$\dfrac{p(p - sH/2)}{1 - sH/2}$	$\dfrac{2pq}{1 - sH/2}$	$\dfrac{q(q - sH/2)}{1 - sH/2}$

A bi-allelic selection model to describe observations of segregation for genes HLA-A and HLA-B in South Amerindians.