# DOES ASSOCIATIVE OVERDOMINANCE ACCOUNT FOR THE EXTENSIVE POLYMORPHISM OF *H-2*-LINKED LOCI?

To determine whether the *H-2* complex in house mice is subject to selection, NADEAU, COLLINS and KLEIN (1982) compared the degree of polymorphism of allozyme-encoding loci linked to the *H-2* complex with the polymorphism of comparable loci located elsewhere in the genome. This comparison was based on the expectation that a process termed hitchhiking (HH) (MAYNARD SMITH and HAIGH 1974; THOMSON 1977) should reduce the polymorphism of neutral loci that are linked to selected loci. (We assumed that allozyme polymorphisms were neutral relative to the *H-2* polymorphisms.) Contrary to expectations, however, *H-2*-linked loci were usually more, rather than less, polymorphic than other loci, suggesting that these neutral loci are not subject to the HH effect. Alternative explanations such as coadaptation of these loci and fortuitous linkage of highly polymorphic loci were discussed but like HH were considered to be unlikely explanations for the extensive polymorphism of *H-2*-linked loci.

SVED (1983) points out that models of associative overdominance (AO) (FRYDENBERG 1963; HILL and ROBERTSON 1968; SVED 1968; OHTA and KIMURA 1970) predict increased polymorphism of neutral loci linked to a selected locus, and he contends that the results described by NADEAU, COLLINS and KLEIN (1982) indicate that *H-2* is subject to balancing selection. AO is an attractive explanation for the polymorphism of *H-2*-linked loci, but before accepting this explanation, we should consider whether AO applies to the *H-2* complex in house mice.

The principal differences between models of HH and AO involve stability of the polymorphisms and population size. HH describes the effects of a selected locus on linked neutral loci during progress of mutant alleles of the selected locus *toward* their equilibrium frequencies, whereas AO describes these effects when alleles of the selected locus are *at* (or near) equilibrium. The effect of HH is most pronounced in large populations but can be effective in small populations if selection is sufficiently strong. By contrast, AO occurs primarily in finite populations in which random events are more likely to produce linkage disequilibrium. Thus, AO requires two conditions: stable polymorphism of the selected locus and small populations. Neither of these conditions are required by HH and neither are thought to occur frequently in house mice. Because of these differences, HH rather than AO was thought to be applicable to the *H-2* loci in house mice.

Although there is no direct evidence that polymorphisms in house mice are stable, *i.e.*, at equilibrium, there is considerable circumstantial evidence that stability is not expected. Mouse populations are often small and frequently consist of fewer than 50 mice (for reviews of the population biology of house mice, see BERRY 1981; SAGE 1981). Population size, however, is known to vary

substantially, sometimes by several orders of magnitude in a single season. In addition, whereas some populations have a social structure in which immigration does not occur, other populations allow immigration; the particular structure adopted by a population depends on population density and environmental conditions such as weather and resource availability. Finally, many populations are not temporally stable. For example, the largest and most stable population found in Southwestern Germany, the BNK population, could not have existed for more than 10 years or about 20–50 generations (NADEAU *et al.* 1981). Under these conditions, founder effects probably exert a considerable influence on the dynamics of polymorphic loci and, therefore, stability of polymorphisms is expected to be rare (*cf.* THOMSON 1977).

The apparent infrequency of gametic disequilibrium within individual populations provides further evidence that mouse populations are not highly structured. Recent evidence suggests that disequilibrium is uncommon, if not rare. For example, while disequilibrium occasionally occurs between the most common *H-2* alleles in certain populations, there is no evidence for disequilibrium for most populations and for most alleles (NADEAU *et al.* 1981). In addition, disequilibrium involving allozyme-encoding loci appears to be rare (BERRY, BONNER and PETERS 1979; BERRY and PETERS 1981; J. BRITTON-DAVIDIAN and J. H. NADEAU, unpublished results). Supporting these observations is the large number of unique *H-2* haplotypes within individual populations (see Table 3 of NADEAU *et al.* 1981). For example, eight of 12 *H-2* haplotypes found in mice in the BNK population were unique, and of the four that were not unique, two were of one type and two of another, even though the loci involved, *H-2K* and *H-2D*, are only about 0.5 cM apart. These results are typical of most populations studied. (We have discounted instances of disequilibrium involving *H-2* alleles found only once in samples from single populations.) The apparent infrequency of gametic disequilibrium even between closely linked loci is consistent with populations in which considerable immigration occurs but not with populations composed of small demes closed to immigration. It is also noteworthy that both HH and AO rely on linkage disequilibrium to provide the connection between the polymorphisms of the selected locus and linked neutral loci. The apparent infrequency of disequilibrium would, therefore, imply that neither HH nor AO accounts for the extensive polymorphism of *H-2*-linked loci.

Further evidence that AO is not a sufficient explanation for the extensive polymorphism of *H-2*-linked loci is obtained by considering the expected magnitude of the effect of AO on the polymorphism of linked neutral loci. Consider the relation $H_{B(A)} \cong [1 + 1/(4N_e c)]H_B$, where $H_B$ is the expected heterozygosity of neutral locus $B$, $H_{B(A)}$ the expected heterozygosity of locus $B$ caused by the cumulative effects of AO involving a number of closely linked selected loci ($A$), $N_e$ the effective population size and $c$ the recombination frequency between $A$ and $B$ (OHTA and KIMURA 1970). We note that *H-2* is a gene complex composed of a number of loci sharing many structural and functional properties and could, therefore, represent the $A$ loci in OHTA and KIMURA'S model. Using $c = 0.05$ [the average recombination frequency between *H-2* and

the linked allozyme-encoding loci used by NADEAU et al. (1981)], we have $H_{B(A)} = 1.2\ H_B$ for $N_e = 25$ and $H_{B(A)} = 1.002\ H_B$ for $N_e = 2500$. Thus, for the values of $c$ and $N_e$ used, AO increases the heterozygosity of a linked neutral locus by a factor of 1.002 to 1.2. By comparison, NADEAU, COLLINS and KLEIN (1982) found that the average heterozygosity of *H-2*-linked loci was twofold higher than the average heterozygosity of loci located elsewhere in the genome. These calculations suggest that only a small fraction of the extensive polymorphism of *H-2*-linked loci could be the result of AO.

The reservations expressed are not meant to imply disagreement with SVED'S argument (1983) that under certain conditions selected loci enhance the polymorphism of linked neutral loci. We believe, however, that the observations mentioned suggest that AO is not applicable to the *H-2* complex and its linked loci in house mice. Until it is demonstrated that AO applies, we should be cautious about accepting AO as an explanation for the extensive polymorphism of *H-2*-linked loci. It should be noted that the effect of *H-2* on the polymorphism of linked loci may represent a special case not necessarily described by HH or AO. *H-2* appears to be subject to a unique combination of pressures, including frequency-dependent selection, negative assortative mating, heterogeneous environments and high mutation rate (WAKELAND and NADEAU 1980; TREISMAN 1981; KLEIN and FIGUEROA 1981; NADEAU, COLLINS and KLEIN 1982, and references therein). The development of models that describe the effect of loci such as *H-2* on the polymorphism of linked loci represents an important unsolved problem.

## LITERATURE CITED

BERRY, R. J., 1981 Population dynamics of the house mouse. Symp. Zool. Soc. (Lond.) **47:** 395–425.

BERRY, R. J., W. N. BONNER and J. PETERS, 1979 Natural selection in house mice from South Georgia (South Atlantic Ocean). J. zool. **189:** 385–398.

BERRY, R. J. and J. PETERS, 1981 Allozymic variation in house mouse populations. In: *Mammalian Population Genetics*, Edited by M. H. SMITH and J. JOULE. University of Georgia Press, Athens.

FRYDENBERG, O., 1963 Population studies of a lethal mutant in *Drosophila melanogaster*. I. Behavior in populations with discrete generations. Hereditas **50:** 89–116.

HILL, W. G. and A. ROBERTSON, 1968 Linkage disequilibrium in finite populations. Theor. Appl. Genet. **38:** 226–231.

KLEIN, J. and F. FIGUEROA, 1981 Polymorphism of the mouse *H-2* loci. Immunol. Rev. **60:** 23–57.

MAYNARD SMITH, J. and J. HAIGH, 1974 The hitchhiking effect of a favorable gene. Genet. Res. **23:** 23–35.

NADEAU, J. H., R. L. COLLINS and J. KLEIN, 1982 Organization and evolution of the mammalian genome. I. Polymoprhism of *H-2* linked loci. Genetics **102:** 583–598.

NADEAU, J. H., E. K. WAKELAND, D. GÖTZE and J. KLEIN, 1981 Population genetics of the *H-2* polymorphism in European and North African populations of the house mouse (*Mus musculus*). Genet. Res. **37:** 17–31.

OHTA, T. and M. KIMURA, 1970 Development of associative overdominance through linkage disequilibrium in finite populations. Genet. Res. **16:** 165–177.

SAGE, R. D., 1981 Wild mice. In: *The Mouse In Biomedical Research*, Edited by H. L. FOSTER, J. D. SMALL, J. G. FOX. Academic Press, New York.

SVED, J. A., 1968 The stability of linked systems of loci with a small population size. Genetics **59:** 543–563.

SVED, J. A., 1983 Does natural selection increase or decrease variability at linked loci? Genetics **105:** 239–240.

THOMSON, G., 1977 The effect of a selected locus on linked neutral loci. Genetics **85:** 753–788.

TREISMAN, M., 1981 The significance of immunity restriction by the major histocompatibility complex, and of the occurrence of high polymorphism at MHC loci: two hypotheses. J. Theor. Biol. **89:** 409–421.

WAKELAND, E. K. and J. H. NADEAU, 1980 Immune responsiveness and polymorphism of the major histocompatibility complex: an interpretation. In: *Strategies of Immune Regulation*, Edited by E. SERCARZ and A. CUNNINGHAM. Academic Press, New York.

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