LETTER

REPLY TO HEDRICK AND KLITZ:
High haplotype discovery rate in the HLA locus

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We have recently shown in 2 large-scale surveys (1, 2) that human leukocyte antigen (HLA) haplotypes frequency distributions are better characterized by purifying selection than by balancing selection. In their Letter, Hedrick and Klitz claim that the HLA locus is a classical example of balancing selection and that our recent results contradict this traditional view (3). They criticize 3 main aspects of our analyses:

1) That the population dynamics parameters are derived from the population properties, and not from an a priori estimate, the principal objection being against the high haplotype creation rate estimated in our analysis;
2) The details of the model, specifically, the choice of new haplotype fitness distribution and the proposed models for genotype fitness;
3) That the results obtained for the 5-locus haplotype are in contrast with their previous results on low-resolution single alleles or allele pairs.

We agree with point 3. Indeed, there is a substantial difference between the dynamics of single alleles and the dynamics of haplotypes and genotypes. From our results, the HLA locus is a clear-cut case of population dynamics that cannot be explained at the single-allele level. At the single allele level, our analysis, performed on large-scale populations and with a high-resolution HLA allele definition, actually shows a small deviation from neutrality toward balancing selection (1, 2), at least, in some populations, as proposed in the seminal work of Hedrick and Thomson (4). Our results are based on both traditional metrics, such as the deviation of homozygosity from the neutral expectation, and simulations. However, in many other populations, the allele dynamics is consistent with a purely neutral model.

We do not believe that points 1 and 2 invalidate our conclusions. Analysis of haplotypes reveals the opposite trend, with a highly significant excess of haplotype homozygotes, as computed from the frequency distribution assuming Hardy–Weinberg equilibrium, or from the estimate of haplotype pairs in genotypes (1, 2); thus, all classical measures of support purifying selection at the level of haplotypes. This conclusion is highly robust to model details and stems, simply, from the excess homozygote frequency. The specifics of the models can be debated, but multiple metrics all reveal a fitness advantage of existing (frequent) haplotypes over new ones.

An unexpected outcome of our analysis is the deviation of the haplotype discovery rate from the current recombination rate estimates in chromosome 6 (5). The estimated haplotype creation rate is indeed extremely high (10 to 30%). This discovery rate includes 2 main components, creation of new haplotypes and haplotype flow between populations. New haplotypes result from mutations and recombination, with the latter estimated to be much more frequent than the former (6). In contrast with early studies, we analyzed self-identified populations that are affected by a strong gene flow (7), which can explain most of the haplotype creation rate. However, even in inbred populations, such as Korean and Japanese, we observed a high haplotype discovery rate. Thus, indeed, the current study suggests a much higher recombination rate than the current estimates. Based on these results, we expect the HLA locus to be a recombination hot spot.

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