LETTER

Evolution of the human MHC: New haplotype frequency analysis is not informative

Philip W. Hedrick[a,1] and William Klitz[b]

The genes in the human leukocyte antigen (HLA) (human major histocompatibility complex [MHC]) complex are iconic examples of balancing selection (1–3). Two important HLA signatures, the retention of alleles, polymorphism, and haplotypes over evolutionary time, known as transspecies polymorphism, and dN/dS > 1 and the related high polymorphism at functionally important amino acids sites, are fundamental aspects of HLA variation. Using simulation, Lobkovsky et al. (4) examined the causes of variation at the highly variable HLA loci in a large database. However, their results are not consistent with either transspecies polymorphism because of the short observed life of haplotypes or dN/dS > 1 because of the low expected amount of variation, even though they claim to "explain [the] evolution of human MHC." Their article causes more confusion than enlightenment about selection at HLA for the following reasons:

1) The modeling approach of Lobkovsky et al. (4) is inappropriate, that is, the authors examined what levels of recombination and gene flow provided the best fit to 5-locus haplotype frequency data from different populations, given various selection models. There are good empirical estimates of HLA recombination, and gene flow estimates could be obtained from neutral loci. These values should be used and the "haplotype discovery rate," which combines recombination and gene flow, should not be estimated from their simulations. For the best fit to their selection models, Lobkovsky et al. (4) found that insupportably high haplotype discovery rates of 10 to 25% new haplotypes each generation were necessary (they cite a report that recombination could only account for 3% of the novel haplotypes). This very high rate appears to obscure any signal of balancing selection.
2) New haplotypes were generated by Lobkovsky et al. (4) with the infinite-alleles model where new haplotypes are given a random fitness between 0 and 1. This ignores the specific alleles at the 5 different loci that make up the haplotypes, many of which are probably present because of previous selective advantage. Lobkovsky et al. (4) used a multiplicative fitness model, where heterozygotes can have a very low fitness, given one low-fitness haplotype and rapid decay of new haplotype fitnesses to 0 in 3 to 20 generations. There is no direct support for either assumption (2, 3, 5).
3) The results (4, 6) obtained for 5-locus HLA haplotypes are very different from those found previously for single or pairs of HLA loci because they reject neutrality in favor of nonbalancing selection, not in favor of balancing selection. A number of studies (6–8) have shown a more even distribution of HLA allele frequencies than expected given neutrality. Alter et al. (6) also found this pattern for pairs of HLA loci, consistent with the finding by Hedrick and Thomson (9) that HLA linkage disequilibrium was higher than expected given neutrality. Furthermore, the combined action of selection and recombination over time on linkage disequilibrium is consistent with the pattern produced by selection favoring a variant at these loci and consequently the linked associated haplotype (10), a scenario not explored by Lobkovsky et al. (4).

An analysis using this database, known recombination rates, directly estimated gene flow rates, and an appropriate mutation model could provide insight into the selective mechanisms operating on HLA haplotypes.

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[a]School of Life Sciences, Arizona State University, Tempe, AZ 85287; and [b]Department of Integrative Biology, University of California, Berkeley, CA 94720

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[1]To whom correspondence may be addressed. Email: philip.hedrick@asu.edu.
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