Letters to the Editor

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Reply to Gill

To the Editor:

The "alternative approach" to our analysis (Ober et al. 1997) proffered by Gill has two parts: (1) "genes linked to the genes encoding HLA antigens, and not the HLA antigens themselves, are involved in these associations"; and (2) "the potential association between HLA and mate choice may reside in the HLA-B-DR-DQ region." In reply, we cite the first sentence of the final paragraph of our paper: "In summary, these data are consistent with the conclusion that genes in the HLA region may influence mate choice in humans" (Ober et al. 1997, p. 503).

We see no conflict between the data showing decreased HLA haplotype matching between Hutterite mates (Ober et al. 1997) and the absence of decreased allele matching at the *HLA-A* or *HLA-B* loci in South Amerindians (Hedrick and Black 1997). Indeed, among the same 411 Hutterite couples studied for HLA-haplotype matching, there was no significant evidence favoring decreased allele matching at the *HLA-A, HLA-B,* or *HLA-DR* loci, as shown in table 1. (The nonsignificant decrease in the number of observed allele matches at each of the three loci is consistent, in a population with a limited repertoire of haplotypes, with the significant HLA-haplotype effect on mating structure reported.) That any single HLA locus or other locus in the HLA region would, per se, be critical to mate choice seems unlikely, since this would represent a very narrow evolutionary strategy for avoidance of homozygosity; rather, we suggest that it is the haplospecific configurations of alleles—that is, haplotypes—that is essential to the decreased between-mate haplotype matching that we reported.

We cannot determine, on the basis of the Hutterite data, whether the *HLA-B–HLA-DR* segment or the *HLA-DQ* segment may be more important than adjacent major-histocompatibility-complex (MHC) regions in this respect, but we do disagree that exclusion of the *HLA-A* locus from the haplotype-matching analysis—even if only the *HLA-B–HLA-DQ* region were relevant to mate choice—would have increased the statistical significance of our findings. The Hutterite genealogy was founded by 62 progenitors ~12 generations ago. Given a 1% recombination frequency between *HLA-A* and *HLA-B,* it is likely that haplotypes identical by state (IBS) for *HLA-B, HLA-DR,* and *HLA-DQ* alleles but with different *HLA-A* alleles are not identical by descent (IBD). Among the 48 ancestral five-locus (*HLA-A, HLA-C, HLA-B, HLA-DR,* and *HLA-DQ*) haplotypes, there were 35 unique three-locus (*HLA-B, HLA-DR,* and *HLA-DQ*) haplotypes (see Kostyu et al. 1993, table 3). *HLA-B–HLA-DQ* haplotypes that were IBS but not IBD might differ—and, in our judgment, are likely to differ—at unknown loci within the *HLA-B–HLA-DQ* segment. Thus, we concluded that, in the Hutterite genealogy, *HLA-A* allelic variability might serve as a proxy for allelic variability in other parts of the haplotype, including but not limited to the *HLA-B–HLA-DQ* segment.

To address this question, we have since typed the 48 serologically defined ancestral five-locus haplotypes by molecular methods and for 11 additional MHC loci, including four loci—*TNFa, BF, C4A,* and *C4B*—located between *HLA-B* and *HLA-DR* (authors' unpublished data). On the basis of these new results, the number of unique ancestral five-locus haplotypes was revised from 48 to 47, but the number of unique three-locus haplotypes remained unchanged, at 35. Therefore, there were 12 three-locus haplotypes that were IBS but that, on the basis of *HLA-A* allelic differences, probably were not IBD with other identical three-locus haplotypes. Ten of these 12 three-locus IBS haplotypes have now been shown to have different alleles at loci within the *HLA-B–HLA-DR* segment, thereby verifying the supposition that the *HLA-A* locus was indeed a good proxy for variability within the *HLA-B–HLA-DQ* segment. In addition, 3 of the 47 *five-locus* IBS haplotypes were shown to be distinguishable by typing for loci within the *HLA-B–HLA-DQ* segment. Another 2 of the 47 IBS haplotypes were split by typing for *HLA-G* (telomeric to *HLA-A*) and for *LMP7, TAP1, LMP2,* and *HLA-DPB1* (centromeric to *HLA-DQ*). The newly refined haplotype data continue to show decreased HLA haplotype matching between spouses, providing, in the context of no significant decrease in allele matching at *HLA-A, HLA-*

Table 1

Expected and Observed Numbers of Couples Matching for an HLA Allele

Locus	No. Expected[a]/No. Observed	χ^2_4	*P*
HLA-A	207.0/198	.789	.37
HLA-B	151.8/143	.809	.37
HLA-DR	184.5/178	.416	.52

[a] Calculated by method 1 of Ober et al. (1997).

B, or *HLA-DR*, support for the argument that it is the haplospecific configuration of alleles at all (or at least many) of the loci in the MHC region, not allelic differences at individual HLA loci, that is important.

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