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HLA and Mate Choice in Humans

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Summary

Evidence from studies in rodents suggests that mate selection is influenced by major-histocompatibility-complex haplotypes, with preferences for dissimilar partners. This study was initiated to determine whether avoidance of a mate with the same HLA haplotype as one's own might be occurring in the Hutterites, a North American reproductive isolate of European ancestry, notable for their large sibships, communal lifestyle, and limited number of five-locus HLA haplotypes (HLA-A, -B, -C, -DR, and -DQ). HLA haplotypes were known for 411 Hutterite couples. The number of couples expected to match for a haplotype was calculated in two ways: first, from population genotype frequencies, with account being taken of the nonrandom mating pattern with respect to colony lineages, and, second, from computer simulations using conservative founder assumptions and the exact genealogy of the 411 couples. We observed fewer matches for HLA haplotypes between spouses than expected (first method, $P = .005$; second method, $P = .020–.067$). Among couples who did match for a haplotype, the matched haplotype was inherited from the mother in 29 cases and from the father in 50 cases ($P = .018$). These results are consistent with the conclusion that Hutterite mate choice is influenced by HLA haplotypes, with an avoidance of spouses with haplotypes that are the same as one's own.

Introduction

Mate choice based on recognizable characteristics with a genetic component, such as stature, IQ, blindness, coronary risk factors, and head shape, is well established in humans (reviewed in Cavalli-Sforza and Bodmer 1971; Vogel and Motulsky 1996). In the mouse, a more direct effect of genes on mate choice has been proposed for major histocompatibility complex (MHC) loci; in inbred and seminatural populations there is a preference for mates with MHC types different from either one's own or a foster parent's strain (Yamazaki et al. 1976, 1978, 1988; Egid and Brown 1989; Potts et al. 1991). Avoidance of mates with similar MHC types would facilitate the avoidance of mating with relatives—and the deleterious effects of inbreeding that may result. Data on MHC-based mate choice, from outbred, ethnically heterogeneous human populations, have been inconclusive because of the confounding effects of ethnic and racial self-preference (Pollack et al. 1982; Rosenberg et al. 1983; Jin et al. 1995). The present study was initiated to determine whether HLA-based mate choice might be detectable in an inbred, ethnically homogeneous population with a limited repertoire of HLA genes.

The null hypothesis that HLA genes do not influence mate choice was tested in the Hutterites, a Caucasian religious isolate living in the northern United States and western Canada. First we compared the observed number of couples matching for an HLA haplotype with an expected number, by two different methods, as discussed below. Second, we noted whether the matched haplotypes were equally likely to be inherited from the mother or the father. Third, we examined the haplotype composition of the matched haplotypes, hypothesizing that the frequency of specific haplotypes among the matched haplotypes should reflect the haplotype frequencies of the sampled population.

Subjects and Methods

The Hutterite Population

The modern Hutterite population derives from an Anabaptist religious group established in 1528 in the Tyrolean Alps. Religious persecution necessitated migrations throughout Europe, and in the 1870s ~400 members settled on three communal farms (or colonies) in the area that is now South Dakota (Steinberg et al. 1967; Hostetler 1974). These three colonies are ancestral to each of the >350 contemporary colonies (>35,000 individuals) and are the origin of the three major subdivisions of Hutterite population structure, the Schmiedeleut (S-leut), Leherleut (L-leut), and Dariusleut (D-leut). By 1910 there were four S-leut colonies, which led to four lines of descendent colonies (A–D), termed "clans" by

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Bleibtreu (1964) and referred to as "lineages" in the present report. Today S-leut colonies are located in South Dakota, North Dakota, Minnesota, and Manitoba, and L- and D-leut colonies are located in Montana, Washington, Alberta, and Saskatchewan. The subjects in this study are from 31 of the 44 S-leut colonies in South Dakota (fig. 1). The historical relationship between the 44 contemporary South Dakota colonies and the ancestral S-leut colony is shown in figure 2.

Marriages among Hutterites are patrilocal—that is, wives move to their husband's colony at marriage. Therefore, women may change lineage affiliations at marriage, but men are lifetime residents of the lineage into which they were born. Divorce among Hutterites is strictly prohibited; marriages represent lifetime partnerships. Most Hutterites marry in their early 20s after courtships that last ⩾1 year. After completing school (at age 15 years) and prior to marriage, Hutterites often visit other colonies to assist with farm (men) or household and gardening (women) chores, to help a sister after the birth of a child (women), or to attend a sister's wedding in her husband's colony (men and women). Such visits allow Hutterites to meet potential spouses outside their own colonies. Marriages are not prescribed. However, Hutterites tend to visit colonies that have recent historical relationships to their own colony. Thus it is not surprising that many marriages are endogamous with respect to colony lineage (Bleibtreu 1964; O'Brien 1987). Furthermore, it is common for more than one marriage to occur between two sibships. For

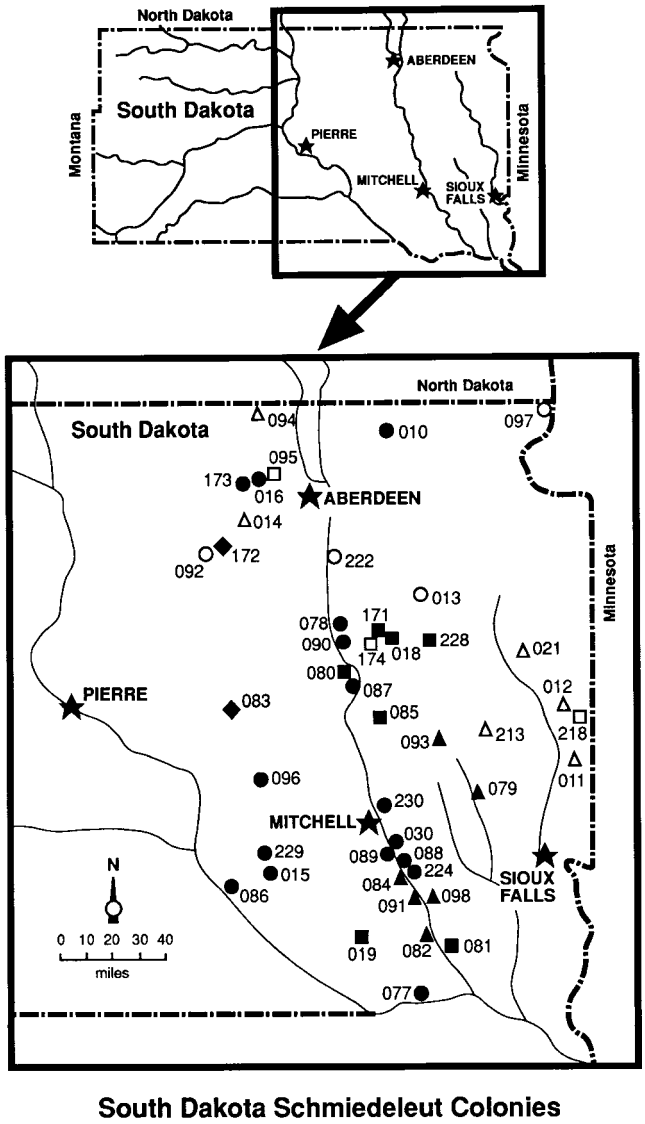

Figure 1 Location of all 44 S-leut colonies in South Dakota. Closed symbols are colonies that were visited during these investigations (circles denote lineage A; squares denote lineage B; triangles denote lineage C; and diamonds denote lineage D).

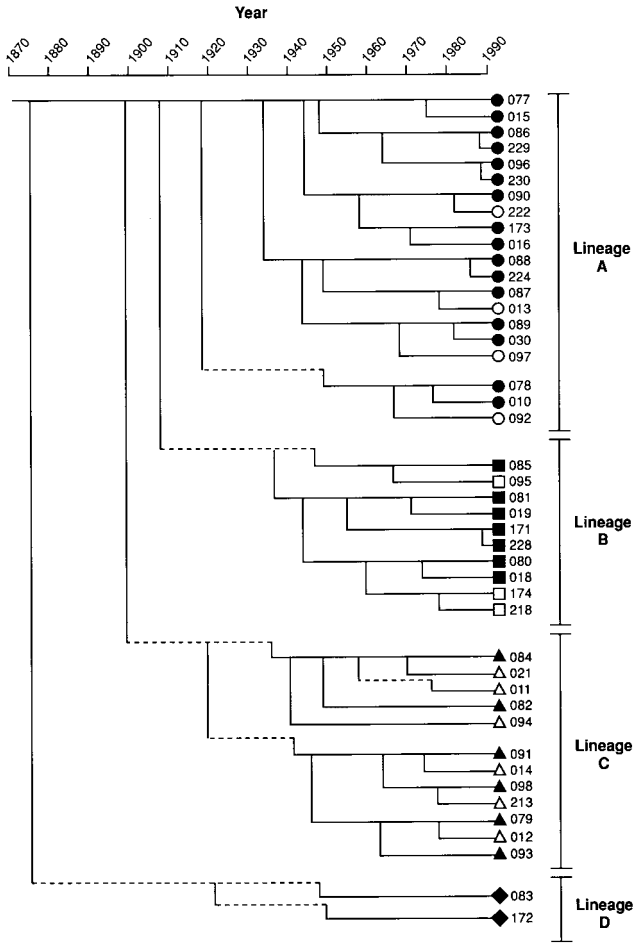

Figure 2 Historical relationship between the founding S-leut colony (077) and derivative South Dakota S-leut colonies. The dates at the top are the dates of the fission from the parent colony. Dotted lines indicate that there are branches to Manitoba S-leut colonies that are not shown in the figure. The four S-leut colonies present in 1910 represent the ancestral colonies for the four lineages A–D. Colonies that were visited during this study are denoted by blackened symbols (circles denote lineage A; squares denote lineage B; triangles denote lineage C; and diamonds denote lineage D). (fig. is modified from O'Brien 1987)

example, in 1960, of 812 marriages, 20% were "double" (Mange 1964); that is, either two brothers married two sisters or a brother and a sister married a sister and a brother. An additional 2% of marriages were "triple," and 0.5% were "quadruple." Close inbreeding, including marriage between first cousins, is discouraged and is rare.

Hutterite ancestry can be traced, through genealogical records, to the mid 1700s, when the Hutterites resided in Russia (Mange 1964; Steinberg et al. 1967). Contemporary breeding members of the S-leut population can trace their ancestry to only 68 founders, who were themselves quite possibly related (Mange 1964; Martin 1970). Because of the small number of founders, the average (±SD) kinship coefficient among living South Dakota S-leut couples is .0369 (±.013), greater than that of first cousins once removed (Ober et al. 1992).

Sample Composition

Since 1982, 31 (70%) of the 44 S-leut colonies in South Dakota were visited as part of our ongoing studies of HLA and fertility (Ober 1995) (fig. 1). Colonies representing all four lineages of colony descent were selected. Our sample included 16 (80%) of 20 colonies from lineage A, 7 (70%) of 10 from lineage B, 6 (50%) of 12 from lineage C, and 2 (100%) of 2 from lineage D (table 1).

Within each colony, all married adults were asked to participate in our studies. Blood samples for HLA typing were collected from all cooperative adults. Laboratory techniques for HLA typing have been described elsewhere (Kostyu et al. 1989). Participation within each colony was 18%–100% of married couples (mean 75%). Five-locus HLA haplotypes were determined by serology or by DNA typing for both partners in 411 marriages. In this sample of married adults, there were 48 "ancestral" haplotypes and 11 haplotypes that were observed to be recombinants (Kostyu et al. 1989). Prior to marriage, the wives in this sample were residents of S-leut colonies in South Dakota ($N = 392$), Manitoba ($N = 14$), and Minnesota ($N = 5$). The proportion of couples sampled from South Dakota colonies that belong to each lineage is shown in table 1. The median birth year for wives in the sample was 1950 (range 1900–75), and the median year of marriage was 1971 (range 1920–95).

Table 1

Sample Composition with Respect to Colony Lineage

Lineage	No. of Colonies Sampled/ No. of South Dakota Colonies (Proportion)	No. of Couples Sampled/ No. of Couples Present (Proportion)
A	16/20 (.80)	206/252 (.82)
B	7/10 (.70)	90/128 (.70)
C	6/12 (.50)	84/120 (.70)
D	2/2 (1.0)	31/45 (.69)
	31/44 (.70)	411/545 (.75)

Table 2

Colony Residence at Birth, by Lineage, for 411 Husband-Wife Couples

Wife's Lineage	Husband's Lineage[a] A	B	C	D	Total
A	115 (60)	33	24	14	186
B	35	33 (26)	10	0	78
C	43	19	42 (24)	1	105
D	13	5	8	16 (12)	42
Total	206	90	84	31	411

[a] Numbers in parentheses are number of marriages in which partners were born into the same colony.

Calculation of the Expected Number of Couples Randomly Matching for HLA Haplotypes

We proposed that mate choice might involve avoidance of a spouse with a haplotype the same as one's own haplotype. To test this proposal, an estimate of the expected number of couples matching for an HLA haplotype, an estimate based on the nonrandom but presumably non–HLA-associated mating predicted on the basis of Hutterite population structure, was determined. Hutterite marriage patterns include patrilocal residency, close-inbreeding avoidance, colony-lineage endogamy, and multiple marriages between sibships. The net effect of these factors on the expectation for the number of couples randomly matching for one or more HLA haplotypes is not immediately clear.

In outbred human populations, mating is often assumed to be random with respect to the genes in the population. The random expectation for mating-type frequencies can then be calculated from population gene or genotype frequencies. However, mate choice in humans is never truly random with respect to genes. In many populations, close inbreeding is avoided; in other populations, distant relatives are preferred (for examples, see Vogel and Motulsky 1996, pp. 552–559). First-cousin marriages are uncommon in the Hutterites (there were none among the 411 couples in this sample). Avoidance of first cousins or other close relatives decreases the likelihood that a partner with the same HLA haplotype will be chosen, compared with expectation based on random mating within the S-leut. On the other hand, marriage with a more distant relative, particularly a person from the same lineage, is common. The lineage affiliations of the colonies of birth of the 411 husbands and 411 wives in our sample are shown in table 2. Two hundred six (50%) marriages were endogamous with respect to lineage, of which 122 (30%) were endoga-

mous with respect to colony of birth. As would be expected on the basis of Hutterite population structure, frequencies of the five-locus HLA haplotypes were different among the four lineages (table 3). Thus, lineage endogamy increases the likelihood that one will meet a partner with the same haplotype, compared with expectation based on random mating throughout the S-leut.

Hutterite sibships are large (median completed family size is eight), and not infrequently more than one marriage occurs between two sibships. In our sample of 411 marriages, 89 involved multiple marriages between two sibships. Sixty-eight of these were doubles—that is, there were 34 instances of two marriages between two sibships. Twelve marriages were triple (three marriages between four sibships), four were quadruple (four marriages between two sibships), and one was quintuple (five marriages between two sibships). In 2 of the 89 multiple marriages, a man married the sister of his deceased wife. The social and genetic factors that influenced mate choice in these 89 marriages might differ qualitatively or quantitatively from factors that influenced mate choice in the remaining 312 marriages. Certainly, the second marriage between siblings from two sibships is not totally independent genetically from the first marriage, but the effect of multiple marriages on the likelihood that one will choose a partner with the same haplotype as one's own cannot be predicted.

Our null hypothesis was that the number of couples in which the spouses matched for an HLA haplotype would not differ from expectation derived from a consideration of the aforementioned mating pattern in the Hutterites—that is, that mate choice was not influenced by characteristics intrinsic to the genes in the HLA region of chromosome 6. First, the expected number of marriages in which spouses match for an HLA haplotype was calculated separately for each of the 15 categories of mating (table 2). We considered each of the HLA haplotypes as an "allele" and then used male "genotype" frequencies of the husband's lineage and female "genotype" frequencies of the wife's lineage, to estimate the expected number of matched haplotypes. We did not use HLA-haplotype frequencies, assuming Hardy-Weinberg equilibrium, because of the previously reported deficit of haplotype-homozygous persons (Kostyu et al. 1993).

As a second estimate of the number of couples expected to match for an HLA haplotype, we conducted computer simulations using the exact genealogy of the sampled population of 411 couples. This genealogy contained 1,891 individuals. All sampled individuals were traced back to 62 progenitors (62 of the 68 founders of the contemporary S-leut population). Although the relationships between the progenitors are unknown, it is likely that some were related to each other; for example, there have been only 15 surnames in the population since at least the early 1700s, suggesting that there were 15 male founders. It is presumed that the founders were unrelated, but they may have been related to each other through female lines. Thus, we believe that there were $\leq$30 unrelated haplotypes among the male founders. The number of female founders is more difficult to estimate; but it may have been greater than the number of

Table 3

HLA-Haplotype Frequencies for 822 Married S-leut Hutterites, by Lineage at Birth

MHC Haplotype	HLA-Haplotype Frequency When Lineage at Birth Is[a]			
	A (N = 784)	B (N = 336)	C (N = 378)	D (N = 146)
A2-Cw3-B62-DR4-DQ3	.068	.051	.095	.034
A3-Cw4-B35-DR1-DQ1	.075	.069	.066	.096
A1-Cw6-B57-DR7-DQ3	.046	.030	.119	.110
A32-Cx-B35-DR5-DQ3	.032	.125	.085	.027
A26-Cx-B38-DR2-DQ1	.059	.074	.053	.041
A24-Cx-B51-DR10-DQ1	.085	.012	.011	.027
A24-Cw7-B8-DR3-DQ2	.052	.074	.005	.027
A2-Cx-B51-DR6-DQ1	.080	.036	.011	.089
A2-Cw1-B27-DRw8-DQx	.047	0	.079	0
A3-Cw2-B27-DR1-DQ1	.046	.009	.003	.075
A24-Cw3-B60-DR2-DQ1	.023	.015	.066	.014
A2-Cw4-B62-DR1-DQ1	.012	.063	.056	.041
A3-Cx-B51-DR4-DQ3	.034	.060	.008	.021
A2-Cw2-B51-DR4-DQ3	.056	0	0	0
A31-Cw5-B51-DR6-DQ1	.012	.024	.008	.055
A3-Cw7-B7-DR4-DQ3	0	.057	0	0
All others	.273	.301	.335	.343

Note.—Haplotypes for which the frequency was $\geq$.05 are shown.

[a] N = number of haplotypes.

male founders, because it was not uncommon for females to die early (e.g., in childbirth) and for widowed males to remarry once or even twice. We conclude that the number of female ancestors was likely to have been >15, but many of these females may have been related themselves. Thus, the number of unrelated haplotypes in the founders was ⩾48, the number of "ancestral" haplotypes observed, but possibly ~60 (equal to 15 male and 15 female founders) and very likely <80 (1.67 times as many female as male founders).

In the simulations, each of the 48 "ancestral" haplotypes was included in the set of haplotypes assigned to the 62 progenitors; the remaining haplotypes in the progenitors were selected from a data set of "European" haplotypes. (A list of 1,000 haplotypes was compiled from unrelated individuals of European ancestry that were HLA typed in L.R.W.'s laboratory. This list contained 571 unique haplotypes and included 24 of the 48 ancestral Hutterite haplotypes.) In the first set of simulations, the number of unique haplotypes was assumed to be 60 (corresponding to 30 unrelated S-leut founders who were ancestral to the progenitors), so the total number of unique haplotypes randomly selected from the European data set was 12. These 60 haplotypes were each distributed at random to the progenitors, so that each haplotype was present in the progenitor haplotypes. Then the remaining 64 haplotypes were chosen randomly, with replacement from the set of 60 haplotypes. In the second set of simulations, the number of unique haplotypes in the progenitors was 70 (corresponding to 35 unrelated founders), and in the third set of simulations the number of unique haplotypes in the progenitors was 80 (corresponding to 40 unrelated founders). The total numbers of unique haplotypes selected from the European data set in the second and third simulations were 22 and 32, respectively. The haplotypes were allowed to segregate through the genealogy in a random fashion, allowing for recombination in 0.9% of meioses (0.4% between A and C; 0.5% between B and DR) (Dawson et al. 1995); each set of simulations was repeated 1,000 times. After each simulation, the same 411 spouse pairs in our study were sampled from the simulated population, and the number of spouses matching for one or more haplotypes was counted.

Parental Origin and Antigenic Composition of the Matched HLA Haplotype

As a second test of the null hypothesis that HLA-region genes have no effect on mate choice, we tablulated the sex of the parent of origin for each haplotype for which there was a match between spouses; that is, on those occasions when spouses did match for the same five-locus HLA haplotype, we determined whether that haplotype was inherited from the spouse's mother or father. The expectation, based on Mendelian gene-transmission probabilities, is that any haplotype is equally likely to be derived from the mother or father. However, peculiarities of Hutterite population structure, other than an effect of HLA-region genes, might cause a deviation from this random expectation. To test for this, the sex of the parent of origin of each of the matched haplotypes was tabulated for each of the simulations described above. A third test of the null hypothesis was to determine whether the frequency of each of the matched haplotypes corresponded to the frequency of that haplotype in the population as a whole.

Table 4

Expected and Observed Numbers of Couples Matching for a Haplotype

A. Method 1		
No. of Couples Matching		
Expected	Observed	*P* Value
64.76	44	.005[a]
B. Method 2		
No. of Unique Haplotypes in Progenitors	Mean (±SD) No. of Couples Matching[b]	Empiric *P* Value[c]
60	63.6 (±11.3)	.020
70	60.5 (±10.2)	.035
80	59.1 (±10.7)	.067

[a] Because of lack of independence among multiple marriages, the significance level may be overestimated (the 44 couples included 13 couples from multiple marriages); however, if only the 322 single marriages are included, there are 31 matches observed (50.1 expected; goodness of fit $\chi^2 = 10.489$; $P = .0012$).

[b] Based on 1,000 computer simulations.

[c] Probability of observing ⩽44 couples matching for a haplotype.

Results

HLA-Haplotype Matching

Among the 411 couples in this study, 41 matched for one haplotype and 2 matched for two haplotypes; in one additional couple the husband was homozygous for a haplotype that matched one of the wife's haplotypes (44/411 = 10.7% of couples matched for one or more haplotypes). The expectation for the number of couples matching was derived separately for each of the four within-lineage mating groups and for each of the 11 categories of between-lineage mating (table 2), on the basis of male and female genotype frequencies for each lineage. The 44 couples that matched for an HLA haplotype were significantly fewer than the 64.76 expected (goodness of fit $\chi^2 = 7.90$, 1 df; $P = .005$) (table 4A).

As a second method of calculating expectation, we tabulated the number of couples that matched for a

haplotype after each set of simulations (table 4B). When we assumed that there were 60 unique haplotypes in the S-leut population, the mean (±SD) number of couples matching for a haplotype was 63.6 (±11.3), and the empiric probability of ⩽44 couples matching for one or more haplotype was .020. When we assumed that there were 70 unique haplotypes in the progenitors, the mean (±SD) number of couples matching for a haplotype was 60.5 (±10.2), and the empiric *P* value was .035. When we assumed that there were 80 unique haplotypes in the progenitors, the mean (±SD) number of couples matching for a haplotype was 59.1 (±10.7), and the empiric *P* value was .067.

Parental Origin of Matched Haplotypes

Avoidance of self-MHC could be influenced by the parental origin of the haplotype (maternally vs. paternally derived haplotypes may have different effects) or the genetic composition of the haplotype (certain haplotypes may be associated with avoidance or nonavoidance). To address these possibilities, we examined the parental origin and the haplotype frequencies of the matched haplotypes.

Among 44 couples matching for haplotypes, there were 46 matched haplotypes in the wives and 47 matched haplotypes in the husbands. (In one couple the husband was homozygous for the matched haplotype; and two couples matched for both haplotypes). Of these 93 matched haplotypes, the sex of the parent from whom the haplotype was inherited could be determined for 79. The matched haplotype was inherited from the mother in 29 and from the father in 50, which deviated significantly both from the equal numbers of 39.5 and 39.5 (goodness of fit $\chi^2 = 5.6$, $P = .018$) and from the average simulated expected number of 39.0 maternal and 40.0 paternal (goodness of fit $\chi^2 = 5.1$, $P = .02$) (table 5). There was no significant difference between husbands and wives (16/43 for husbands vs. 13/36 for wives) with respect to the proportion of times that the matched haplotype was maternally derived, suggesting that both husbands and wives equally avoid partners with a matched maternally inherited haplotype.

Frequency and Parent of Origin of Each Matched Haplotype

The numbers of matched haplotypes among the 10 most common haplotypes, according to whether they were maternally inherited or paternally inherited, are shown in table 6. The observed composition of matched haplotypes was not significantly different than the composition of haplotypes that was expected on the basis of genotype frequencies in this sample (table 6; goodness of fit $\chi^2 = 14.5$, 10 df, $P = .151$). One haplotype, A1-Cw6-B57-DR7-DQ3, was present on 16 paternally inherited matched haplotypes and on 0 maternally inherited matched haplotypes. However, among the eight couples who matched for a paternally inherited haplotype, A1-Cw6-B57-DR7-DQ3, there were four double marriages (two marriages each between two sibships) and three triple marriages (three marriages between two sibships). Thus, the nonrandom distribution of this haplotype among paternally inherited matched haplotypes occurred in a small number of sibships. Two double marriages and the triple marriages were between spouses from lineage C, where this is the most common haplotype. The other two double marriages were between partners from lineages A and B, where this haplotype is less frequent (table 3). The absence of this haplotype among the maternally inherited haplotypes, however, suggests the possibility that it may be avoided when it is maternally derived. For the other matched haplotypes there were no outstanding differences between the proportions that were paternal or maternal in origin.

Table 5

Sex of Parent of Origin of Matched Haplotype

No. of Unique Haplotypes in Progenitors	Mean (±SD) No. of Matched Haplotypes Inherited From	
	Mother	Father
60	63.4 (±12.4)	64.8 (±13.1)
70	60.5 (±11.6)	61.9 (±11.8)
80	59.1 (±12.0)	60.5 (±12.4)

Note.—For 79 matched haplotypes in our sample, the parent of origin was the mother in 29 cases and was the father in 50 cases; this is different from the expected, equal numbers of 39.5 and 39.5 ($P = .018$) and from the average distribution in the simulated samples ($P = .024$).

Discussion

Two lines of evidence from the Hutterites are consistent with the hypothesis that MHC-based mate choice may be operating in humans. First, there were fewer than expected HLA-haplotype matches among spouses, whether expectation was based on (*a*) calculations made from genotype frequencies of the sex and lineage from which the spouse was selected ($P = .005$) or (*b*) computer simulations assuming different numbers of unique haplotypes among the founders but using the exact genealogical structure of our sampled population ($P = .020$–$.067$). The latter experiments demonstrated that the magnitude of the deviation from random expectations is a function of the number of unique haplotypes that were present in the 62 progenitors (who were descendents of the hypothesized founders). As the number of unique haplotypes in the progenitors increases, the number of couples sampled from the simulated population that match for a haplotype decreases. We selected the range of 60–80 as representative of the number of unre-

Table 6

Distribution of Matched Haplotypes, According to Whether They Were Maternally or Paternally Inherited

HLA Haplotype	No. of Matched HLA Haplotypes			No. of Haplotypes	
	Paternally Inherited	Maternally Inherited	Origin Unknown	Observed	Expected[a]
A2-Cw3-B62-DR4-DQ3	2	6	2	10	11.0
A3-Cw4-B35-DR1-DQ1	5	7	2	14	15.0
A1-Cw6-B57-DR7-DQ3	16	0	0	16	13.6
A32-Cx-B35-DR5-DQ3	7	3	2	12	11.4
A26-Cx-B38-DR2-DQ1	4	2	3	9	14.9
A24-Cx-B51-DR10-DQ1	4	2	0	6	7.6
A24-Cw7-B8-DR3-DQ2	0	0	0	0	6.2
A2-Cx-B51-DR6-DQ1	2	2	0	4	10.3
A2-Cw1-B27-DRw8-DQx	2	2	0	4	5.4
A3-Cw2-B27-DR1-DQ1	1	1	0	2	3.2
All others[b]	7	4	5	16	15.4
Total	50	29	14	93	114

[a] Based on genotype frequencies in 411 couples.
[b] Eight couples matched for eight different haplotypes.

lated haploid genomes present in the 62 progenitors. This assumed that the number of unrelated female founders was 1–1.67 times the 15 unrelated male founders, which was based on 15 Hutterite surnames. This assumption appears to be reasonable, because the final number of unique haplotypes, the number of detectable recombinants, and the proportion of rare haplotypes were all within ranges observed in our sample for the simulations using 60–80 unique haplotypes.

The second line of evidence indicating that mate choice is not random with respect to HLA haplotypes comes from those matings in which the spouses did match for an HLA haplotype. In these matings, the matched haplotype was inherited from the father significantly more frequently than it was inherited from the mother ($P = .024$). This is not likely to be an artifact of the population structure, because the matched haplotypes in the simulation studies were inherited nearly equally from the mother and from the father. However, further studies are required to determine whether the striking difference in the parent of origin of the A1-Cw6-B57-DR7-DQ3 haplotype (16 paternal, 0 maternal) is a chance result. In our view, the total data are consistent with mate choice being influenced either by genes in the HLA region or by closely linked genes on chromosome 6, although the magnitude of the effect may be modest.

Mate choice based on avoidance of maternally inherited MHC haplotypes has not previously been reported in humans. MHC-based mating preferences in mice have been observed (Yamazaki et al. 1976, 1978, 1988; Egid and Brown 1989; Potts et al. 1991). Both inbred and seminatural populations of mice preferentially mate with MHC-disparate mice. Furthermore, preferences appear to be acquired postnatally, because mice fostered by allogeneic strains preferentially selected mates who were MHC different from their foster parent's strain but who were MHC similar to their own strain (Yamazaki et al. 1988). On the basis of this observation, Yamazaki and colleagues concluded that MHC-based mate choice in inbred strains of mice is determined by chemosensory imprinting in early life. The greater avoidance of maternally as compared with paternally inherited matched haplotypes in the Hutterites is consistent with this hypothesis, although a "parent of origin" effect, per se, has not been examined in mice.

MHC recognition in mice and rats appears to be olfactory mediated (Yamazaki et al. 1979; Yamaguchi et al. 1981). Urinary-odor differences between strains of mice that differ only with respect to their MHC can be recognized by mice, rats, and even humans (Beauchamp et al. 1985; Gilbert et al. 1986). Mutations at single class I or class II loci result in detectable urinary-odor differences, suggesting that individual odor profiles are a composite of multiple MHC loci (Gilbert et al. 1986; Yamazaki et al. 1990). Although the existence of chemosensory recognition in humans is controversial, human sweat and breast milk may contain cues that provide a basis for discrimination (Porter et al. 1990). Furthermore, a recent study in humans suggests that odor preferences may be HLA linked (Wedekind et al. 1995). The mechanism for HLA-based mate choice in Hutterites is not known, but these data do not rule out the possibility that, in humans, HLA-region genes might influence sensory attributes other than olfaction.

In summary, these data are consistent with the conclusion that genes in the HLA region may influence mate choice in humans. Avoidance of mates with a similar HLA haplotype may be detectable only in populations

with a limited repetoire of haplotypes and reduced variation in factors that could potentially influence human mate choice, such as social status, education, income, and ethnicity. It is not surprising, therefore, that MHC-based mate avoidance has not been detectable in outbred populations, where individuals are unlikely to meet someone with the same haplotype and where many non-genetic factors also influence the selection of mates. Nonetheless, this study suggests that humans are able to discriminate individuals on the basis of genes in the MHC region, as do other mammals.

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