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Studies of HLA, fertility and mate choice in a human isolate

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The role of human leukocyte antigen (HLA) genes in pregnancy and in human mate choice has been investigated in the Hutterites, an inbred population of European origins. High-resolution HLA haplotypes were defined by alleles at 16 loci in >1000 Hutterites. Prospective studies of pregnancy outcome previously demonstrated increased fetal loss rates among Hutterite couples matching for HLA-B antigens ($P = 0.033$) or for the entire 16-locus haplotype ($P = 0.002$). Among living children of couples matching for HLA-B or for the haplotype, there was a non-significant deficit of children who were heterozygous and compatible with the mother; the number of living children who were compatible and homozygous or incompatible and heterozygous was not different than expectations (HLA-B, $P = 0.095$; haplotype, $P = 0.376$). Mate choice among 411 couples was non-random with respect to the HLA haplotype, assessed by a variety of methods ($P = 0.020$ to <0.001). These combined data indicate a role for HLA region genes in both pregnancy outcome and mate choice, and suggest that selection acting on these genes occurs pre-conceptually as well as during pregnancy. This review outlines previously published studies on HLA, fertility and mate choice in the Hutterites.

Key words: fertility/HLA/human inbred population/mate choice

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Introduction

Nearly 50 years after Medawar first proposed the paradox of the fetal allograft (Medawar, 1953), the mechanisms that ensure the survival of allogeneic fetuses remain poorly understood. The notion that histoincompatible fetuses may actually enjoy a selective advantage in pregnancy was first suggested in the early 1960s, and subsequent studies in animal models supported the hypothesis that conceptuses inheriting paternal major histocompatibility (MHC) antigens that differed from maternal antigens (histoincompatible pregnancies) were more likely to survive than conceptuses inheriting paternal MHC antigens that did not differ from maternal antigens (histocompatible pregnancies) (Billington, 1964; Kirby, 1970). By the early 1970s, an analogous role for the human MHC genes—called human leukocyte antigens (HLA)—in pregnancy was proposed (Beer and Billingham, 1976), and evidence demonstrating increased HLA sharing among couples with recurrent spontaneous abortion (RSA) compared with control couples was forthcoming (Komlos *et al*., 1977; Schacter *et al*., 1979). Because only couples who match for HLA can produce compatible fetuses, these studies suggested that maternal–fetal incompatibility with respect to HLA was beneficial in human pregnancy, explaining in part the paradoxical genetic relationship between mother and fetus in pregnancy.

Subsequent studies in couples with RSA provided a cloudy picture of the relationship between HLA sharing and pregnancy outcome, with only about half of the more than 30 published studies demonstrating increased HLA sharing among RSA couples [reviewed in (Ober and van der Ven, 1997)]. It is difficult to reconcile the discrepancies between these studies because of differences in study designs, particularly with respect to the definition of cases and controls, as well as differences in HLA typing methodology. Furthermore, among those studies in which RSA couples shared significantly more HLA than control couples, the actual HLA locus or loci implicated differs among studies.

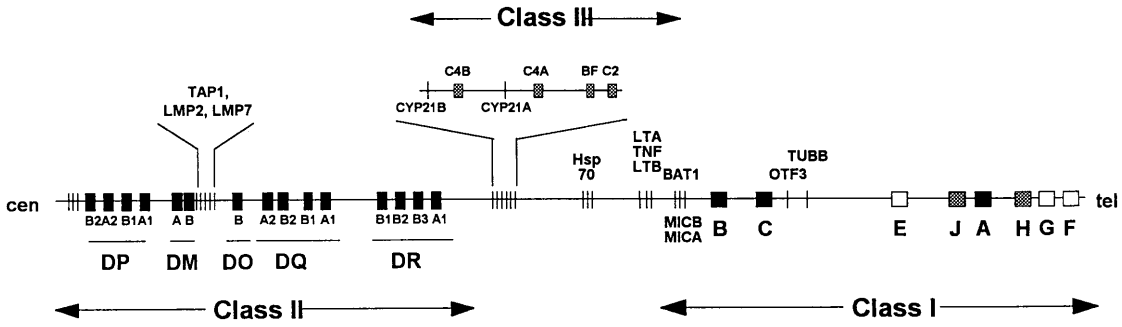

Figure 1. The HLA region on chromosome 6p. HLA loci are shown below the line, and non-HLA loci are shown above the line. The following HLA loci were genotyped in the sample of Hutterites discussed in this article: *HLA-G*, *HLA-A*, *HLA-E*, *HLA-C*, *HLA-B*, *BF*, TNFa, *C4A*, *C4B*, *HLA-DRB1*, *HLA-DQA1*, *HLA-DQB1*, *LMP2*, *TAP1*, *LMP7*, *DPB1*. Reproduced with permission from Ober *et al*., 1998. For additional details on typing methodologies and haplotype frequencies, see Weitkamp and Ober (1999).

To elucidate further the reproductive effects of HLA sharing and to address the limitations inherent in retrospective, case-control studies, we have been conducting prospective, population-based studies in the Hutterites, a religious isolate of European ancestry (Ober *et al*., 1983, 1985, 1992, 1998). These studies have not only demonstrated increased fetal loss rates among couples matching for HLA, but also suggested additional roles for HLA genes in human fertility and mate selection. The following is a review of the previously published studies on HLA, fertility and mate choice in the Hutterites.

The Hutterite population

The 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 approximately 400 members settled on three communal farms (or colonies) in the area that is now South Dakota, USA (Steinberg *et al*., 1967). These three colonies are ancestral to each of the more than 350 contemporary colonies (more than 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). 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, USA. The subjects in our studies are from S-leut colonies in South Dakota.

Due to Hutterite history and pattern of population growth, only a small number of independent genomes are represented in the extant population. For example, the South Dakota S-leut Hutterites in our studies have only 64 founders (Ober and Cox, 1998). In addition, few outsiders have joined the Hutterites since settling in this country. As a result of the small number of founders, the Hutterites are one of the most inbred large populations of European origins (Steinberg *et al*., 1967): the mean inbreeding coefficient in the South Dakota S-leut is 0.031 (SD 0.021), equivalent to that of 1.5 cousins (i.e. first cousins, once-removed) (Ober *et al*., 1998).

The Hutterites live communally on large farms comprised of 10–15 families. As a result, they share a relatively uniform environment, both within and between colonies. On each colony, food is prepared and eaten in a common kitchen. Smoking is prohibited and alcohol consumption is minimal (particularly among women). The communal lifestyle reduces the effects of confounding variables that may affect fertility, such as nutrition, smoking, alcohol consumption and social attitudes toward pregnancy. Hutterite doctrine prohibits contraception, although there is minimal use of contraception among Hutterite women today. Despite this, average family sizes among Hutterites are still large; the median completed family size is nine children among the South Dakota S-leut. Over 1000 adult Hutterites have participated in our studies of HLA and fertility since 1982. All of the married women in this sample (n = 495) have been interviewed and 185 of these women are participating or have participated in a prospective study of pregnancy outcome (described below). HLA haplotypes are known for 1400 Hutterites, including both partners in 411 couples. Initially, 5-locus haplotypes (HLA-A, -C, -B, -DR, -DQ) were defined by serology (Kostyu *et al*., 1989). More recently, molecular and biochemical techniques were used to define all Hutterite haplotypes at 16-loci (Figure 1) (Ober *et al*., 1998; Weitkamp and Ober, 1999). These high-resolution haplotypes have been used to assess the relationship between HLA, fertility and mate choice.

HLA and pregnancy outcome: prospective studies in the Hutterites

Since 1986, Hutterite couples who were still in their reproductive years have participated in a prospective study of pregnancy outcome. The details of this study were described previously (Ober *et al*., 1992, 1998). Briefly, participants were provided with home pregnancy kits and calendar diaries.

They were instructed to test for pregnancy if their periods were a day late, and to record in the diaries the dates of menses, results of pregnancy tests and outcomes of all pregnancies. Data are complete for 251 pregnancies in 111 couples. The mean (± SD) age of the wives in these couples was 28.7 ± 4.8 (range 20–42) years, the couples had a mean of 2.9 ± 2.2 prior pregnancies (range 0 to 9), and 19 couples (17.1%) had experienced a total of 29 fetal losses (Ober *et al*., 1998).

HLA and fetal loss in the Hutterites

The overall fetal loss rate in the prospective study was 15.6% (27 couples experiencing 38 fetal losses). All couples with a loss had at least one prior liveborn child; none had more than two consecutive losses. The mean (± SD) gestational age at the time of the loss was 9.5 ± 3.5 (range 4–19) weeks. The relative frequency of HLA haplotypes did not differ among couples with fetal loss as compared with couples without fetal loss ($P = 0.760$) (Ober *et al*., 1998), indicating that Hutterite haplotypes, *per se*, are not likely to carry abortion-susceptibility alleles or other associated alleles that may predispose to fetal loss (Christiansen *et al*., 1989, 1994). However, the relatively small number of couples with fetal losses would preclude detecting small differences in haplotype frequencies.

Fetal loss rates for couples matching and not matching for HLA loci are shown in Table I. Loss rates were significantly increased among couples matching for alleles at the HLA-B locus ($P = 0.019$) and at the HLA-B flanking loci, HLA-C ($P = 0.033$) and C4 ($P = 0.043$). Matching for alleles at the class II loci (HLA-DRB1, HLA-DQA1, HLA-DQB1, HLA-DPB1) was not associated with fetal loss. However, matching for the entire 16-locus haplotype had the most significant association with fetal loss ($P = 0.002$) (Ober *et al*., 1998).

Table I. Fetal loss rates by HLA matching. The numbers in parentheses are the number of losses/the number of pregnancies. All *P*-values were adjusted for wife's age, wife's inbreeding coefficient and multiple pregnancies per couple. Significant results are shown in bold type. Modified from Ober *et al.* (1998).

HLA locus/region	No. of alleles/haplotypes shared		
	0	≥1	P
A	0.12 (13/106)	0.17 (25/145)	0.537
C	**0.12 (19/156)**	**0.20 (19/95)**	**0.033**
B	**0.10 (16/157)**	**0.23 (22/94)**	**0.019**
TNFa	0.09 (9/100)	0.18 (27/149)	0.078
C4	**0.10 (13/125)**	**0.19 (23/124)**	**0.043**
DRB1	0.15 (20/136)	0.16 (18/115)	0.649
DQA1	0.14 (14/97)	0.16 (24/154)	0.757
DQB1	0.13 (19/145)	0.18 (18/101)	0.344
DPB1	0.13 (12/93)	0.16 (26/158)	0.444
16-locus haplotype	**0.13 (28/221)**	**0.33 (10/30)**	**0.002**

These results indicate that matching for either HLA-B alleles or alleles at an HLA-B-linked locus confers risk for fetal loss in the Hutterites. Molecular subtyping of HLA-B alleles and genotyping for alleles at HLA-B-linked loci should help to discriminate between these two possibilities. In addition, matching for many loci across the haplotype may confer independent risk for fetal loss in this population. However, until additional molecular typing is completed at the HLA-B locus, it is not possible to know whether the haplotype-matching effect is due to matching for alleles at the HLA-B locus or whether matching for alleles at many loci is a separate risk factor for fetal loss. These alternative explanations for these data are discussed elsewhere (Ober *et al*., 1998).

HLA compatibility among surviving children

Increased fetal loss rates among couples matching for HLA-B or for the entire haplotype suggest that compatible fetuses are less likely to survive to term than incompatible fetuses. Therefore, among surviving fetuses (i.e. living children) of Hutterite couples matching for HLA-B or for the entire haplotype there should be an excess of HLA-incompatible children as a result of the selective loss of compatible fetuses. To test the hypothesis that increased fetal loss rates among Hutterite couples matching for HLA resulted in fewer than expected living children who are compatible with mother, genotypes in 370 children of 78 couples matching for HLA-B and 114 children of 28 couples matching for the entire haplotype were examined. Children were classified as to whether they were incompatible (i.e. paternally inherited allele different from both maternal alleles), homozygous-compatible (i.e. paternally inherited allele matches the maternally inherited allele) and heterozygous-compatible (i.e. paternally inherited allele matches the maternally non-inherited allele). Expected numbers of incompatible, homozygous-compatible and heterozygous-compatible children were calculated based on Mendelian segregation ratios in these families. Surprisingly, the observed number of children homozygous for HLA-B or for the haplotype was not different from expectations (HLA-B: 130 homozygotes observed, 112.5 expected; haplotype: 31 homozygotes observed, 29.5 expected). However, the observed number of heterozygous-compatible fetuses was less than expected (HLA-B: 89 heterozygous-compatible fetuses observed, 103.0 expected; haplotype: 23 heterozygous-compatible fetuses observed, 29.5 expected), although the overall differences in deviations from expectations did not reach statistical significance in these samples (HLA-B: $\chi^2_{2df} = 4.7$, $P = 0.095$; haplotype: $\chi^2_{2df} = 1.96$, $P = 0.376$) (Ober *et al*., 1998).

These data suggest that among Hutterite couples matching for HLA-B or for the entire haplotype, fetuses who are heterozygous and compatible (i.e. identical to the mother) are more likely to be aborted than either heterozygous-incompatible or homozygous-compatible fetuses. This unexpected finding may suggest a novel mechanism for fetal loss. Both homozygous-compatible and heterozygous-compatible fetuses should be equivalent from the mother's perspective; i.e. neither would carry antigens that are different from maternal antigens. On the other hand, homozygous-compatible fetuses would recognize maternal cells as non-

self because the mother would carry a second (different) antigen not inherited by the fetus, whereas heterozygous-compatible fetuses would be genetically identical to the mother and not recognize maternal antigens. Thus, these data suggest that HLA incompatibility from the fetus' perspective may be important in pregnancy and not incompatibility from the mother's perspective, as previously thought. This could explain, in part, some of the discrepancies between studies of HLA matching in couples with RSA because the scoring of matches between partners could vary depending on whether the matching is considered from the maternal perspective, the fetal perspective, or both. Regardless, it may be instructive to re-examine some of these data and specifically to examine separately maternal–fetal compatibility from both the maternal and fetal perspectives.

HLA and mate choice in the Hutterites

The lack of a deficit of homozygotes among surviving children of couples matching for HLA was unexpected because it has previously been shown that there are fewer than expected Hutterites who are homozygous for the HLA haplotype at the population level (Kostyu *et al*., 1993; Robertson *et al*., 1999). The analysis of family data discussed above indicates that homozygote deficiencies at the population level are not due to the preferential loss of homozygous fetuses in families of couples matching for HLA. In addition, analytical approaches (Robertson *et al*., 1999) and computer simulation studies (unpublished data) have indicated that the observed deficiencies of homozygotes are not due to the Hutterite population structure *per se*. One potential explanation for the observed homozygous deficiencies at the population level but expected numbers of homozygotes within families is if Hutterite mate choice is non-random with respect to HLA—with preferences for HLA-dissimilar mates.

In inbred and semi-natural murine populations there is a preference for mates with MHC types different from one's own or foster parent's strain (Yamazaki *et al*., 1976, 1978, 1988; Egid and Brown, 1989; Potts *et al*., 1991). It is thought that avoidance of mates with similar MHC types would facilitate the avoidance of mating with relatives and the deleterious effects of inbreeding that may result. MHC recognition in mice and in rats is olfactory-mediated (Yamazaki *et al*., 1979; Yamaguchi *et al*., 1981), and odour differences between mouse strains that differ only with respect to their MHC can be detected by mice, rats, and even humans (Beauchamp *et al*., 1985; Gilbert *et al*., 1986).

To determine whether mate choice in the Hutterites is non-random with respect to HLA, 411 couples in whom HLA haplotypes were known for both partners were studied (Ober *et al*., 1997, 1999). Of these 411 couples, 43 matched for the serologically defined 5-locus haplotype and 35 matched for the high-resolution 16-locus haplotype (Ober *et al*., 1999). Expectations for the number of couples that were expected to match for a haplotype were calculated in two ways. First, the Hardy–Weinberg model of population genetic theory and genotype frequencies in the population was used to estimate the expected number, taking into account the Hutterite preferences for colony lineage endogamous matings. Second, computer simulation studies in the exact Hutterite genealogy were used. These studies take into account all non-random, but non-HLA-associated, aspects of Hutterite mate choice, such as inbreeding avoidance. With both methods, there were significantly fewer Hutterite couples matching for a haplotype than expected [5-locus haplotype: first method, using population genetic theory, $P = 0.0035$; second method, using computer simulations (and assuming 60 unique haplotypes in the progenitors of the pedigree), $P = 0.020$; 15-locus haplotype: first method, $P = 0.0031$; second method, $P < 0.001$] (Ober *et al*., 1997). Furthermore, there was no evidence for avoidance of mates that matched at any particular locus (Weitkamp and Ober, 1998). Thus, these studies suggest that Hutterite mate choice is indeed non-random with respect to HLA haplotypes and that preferences for HLA-disparate mates may account for the deficiencies of homozygotes observed at the population level.

Conclusions

Studies of HLA, fertility and mate choice in the Hutterites have provided novel insights into the effects of HLA matching both prior to conception and during pregnancy. Data derived from prospective studies indicate that matching for HLA-B or HLA-B-linked genes or matching for genes across the entire haplotype is associated with fetal loss (Ober *et al*., 1998). Fewer than expected heterozygous-compatible children of couples matching for HLA-B or for the entire haplotype suggest that maternal–fetal incompatibility from the fetal perspective may be important in human pregnancy (Ober *et al*., 1998). Finally, pre-conceptual selection in the form of HLA-based mate choice, may account for the observation of fewer than expected HLA homozygotes in the population (Ober *et al*., 1997, 1999).

It is noteworthy that among the nearly 500 married women who have participated in our studies, none would fit the definition of RSA (≥3 consecutive spontaneous abortions), and all Hutterite couples with ≥3 spontaneous abortions have had at least two successful pregnancies. Thus, it is not clear whether the HLA-B-associated mechanism of fetal loss in the Hutterites would underlie recurrent or sporadic miscarriage in outbred couples, although associations between HLA-B matching and RSA in outbred populations (Komlos *et al*., 1977; Schacter *et al*., 1979) and between MHC class I antigen matching and sporadic fetal loss in macaques (Knapp *et al*., 1996) have been reported.

The effects of HLA matching on fetal loss and mate choice in the Hutterites could be due to HLA genes *per se* or to as yet unknown, HLA-linked genes. The human MHC contains numerous other genes that could potentially affect reproductive outcome and influence mate choice (Kostyu, 1994; Le Bouteiller, 1994; Fan *et al*., 1996). In fact, other mammalian MHC contain genes that control spermatogenesis, embryo cleavage rates, fetal development and mating preferences (Lyon, 1981;

Warner *et al*., 1987; Potts *et al*., 1991; Uehara, 1991; Chapman and Wolgemuth, 1993; Kirisits *et al*., 1994). Thus, HLA region genes could potentially influence pregnancy outcome and mate choice through a variety of mechanisms. Elucidating these mechanisms may help us to understand the paradox of the fetal allograft as well as factors that maintain genetic diversity at these biologically important loci.

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