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Ancestral and recombinant 16-locus *HLA* haplotypes in the Hutterites

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Abstract Prior studies in the Schmiedeleut Hutterites of South Dakota have demonstrated associations between human leukocyte antigen (*HLA*) haplotype matching and fetal loss (Ober et al. 1992) and mate preferences (Ober et al. 1997), as well as deficiencies of homozygotes for *HLA* haplotypes (Kostyu et al. 1993). These studies were based on the serologically-defined five-locus *HLA-A*, *-C*, *-B*, *-DR*, *-DQ* haplotype. To further elucidate the effects of specific major histocompatibility (MHC) loci or regions on fetal loss and mate choice, we genotyped a sample of Hutterites for 14 MHC loci by DNA or biochemical methods. Typing for additional loci in the *HLA-A* to *HLA-DPBI* region increased the number of recognized Hutterite MHC haplotypes to 67, and further localized the site of crossover in 9 of 15 recombinant haplotypes. Hutterite MHC haplotype sequences are similar to those observed in outbred Caucasians, suggesting that the influence of *HLA* haplotypes on fetal loss and mating structure may be general.

Key words *HLA* · Ancestral haplotypes · Recombinant haplotypes · Hutterites

Introduction

The Schmiedeleut (S-leut) subdivision of the Hutterites, a Caucasian religious isolate that migrated from Europe to the northern United States and Canada in the 1870s, has been the subject of studies of the rela-

tionship between genes in the MHC and reproductive performance (Hauck and Ober 1991; Ober et al. 1983, 1985, 1988, 1992, 1998). The Hutterites are one of the most fertile human populations, having stable marriages, relatively short interbirth intervals, large completed family sizes (median=8), and relatively few (2%) childless couples (Ober 1995; Sheps 1965). Their communal lifestyle ensures that all Hutterites are exposed to similar environments, including a traditional diet, proscriptions on smoking and birth control measures, and only occasional alcohol consumption. Extensive genealogical records indicate moderate remote inbreeding. Although first-cousin marriages are very rare, the average kinship coefficient of mates is 0.0369 (Ober et al. 1992); the S-leut can trace their ancestry to only 68 founders (Mange 1964; Martin 1970).

The small number of founders, who may themselves have been related, suggested that the Hutterites would have limited genetic variability as compared with outbred Caucasian populations – especially for highly polymorphic loci or haplotypes. Indeed, in a sample of 852 S-leut adults who were serologically-typed for five *HLA* loci, *HLA-A*, *-B*, *-C*, *-DR*, and *-DQ*, there were only 48 unique ancestral and 11 contemporary recombinant haplotypes defined through pedigree analysis (Kostyu et al. 1993). Four additional recombinant haplotypes were found in a larger sample of 1082 Hutterites that included children (Dawson et al. 1995).

The small number of *HLA* haplotypes indicates that the Hutterites, as compared with outbred populations, have an increased opportunity to choose a mate with an MHC haplotype identical at all loci between *HLA-A* and *HLA-DQ* by virtue of the haplotypes being identical-by-descent (IBD). Thus, this population provides an unusual opportunity to assess the effect of matching for MHC genes and haplotypes on the choice of a mate and of MHC mating types on the reproductive performance of couples. Based on serologically-defined five-locus haplotypes, we reported decreased fertility among spouses matching for *HLA* antigens (Ober et al. 1992), fewer than expected spouses matching for a ha-

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