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Short Review

New perspectives on mate choice and the MHC

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A long series of studies on mice has shown that mate choice decisions can be made on the basis of individual genotype at the major histocompatibility complex (MHC), which accords well with the importance of immunocompetence in some theories of sexual selection. Recent work on other vertebrate species, including humans, indicates that MHC-based mate choice is not restricted to the genus *Mus*. However, its importance may vary among species as a result of differences in social and mating system structure, and perhaps genome structure. There appears to be a general preference expressed for MHC-dissimilar mates, and such MHC-disassortative mating may be involved in maintaining MHC and/or genome-wide diversity in natural populations. The strength and direction of MHC-based mating preference can vary, and may be modulated by factors such as genetic background, sex, and early life experience.

Keywords: major histocompatibility complex, MHC, mate choice, sexual selection.

The importance placed on immunocompetence in various 'good genes' theories of sexual selection (Hamilton & Zuk, 1982; Folstad & Karter, 1992; Wedekind, 1994; Brown, 1997) has made the idea of a role for major histocompatibility complex (MHC) loci in mate choice attractive to many evolutionary biologists. Initial interest in mate choice and the MHC was further fuelled by speculation that the MHC function in recognition of self/non-self at the molecular and cellular level might be extended to higher levels of biological organization (Thomas, 1975 — cited in Yamazaki *et al.*, 1976). Numerous studies have now shown that MHC genotype is associated with the production of distinctive odours used in individual discrimination by mice, rats and humans (reviewed by Alberts & Ober, 1993; Brown & Eklund, 1994). Kin-recognition, using the MHC as a marker of relatedness, may allow the direction of altruistic acts to increase inclusive fitness (Hamilton, 1964; Manning *et al.*, 1992a). Here we intend to concentrate on those studies dealing directly with MHC-based mate choice, and to examine the factors that modulate the strength and direction of MHC mating preferences. Our review is a synthesis of results from studies on mice and more recent work on humans and other vertebrate species. Although the MHC multigene family is restricted to vertebrates, histocompatibility loci are found in other taxa where they appear to have an analogous role in the regulation of mating systems (Scofield *et al.*, 1982).

Is MHC genotype used in making mate choice decisions?

This question has been addressed mainly by work on mice (Box 1), much of which has relied on the use of MHC-congenic inbred strains which have a specific genetic difference (in this case at the MHC) against an identical genetic background. The first study on mate choice and the MHC was prompted by the fortuitous observation of an apparent MHC-based mate preference in crosses set up to produce MHC-congenic mouse strains (Yamazaki *et al.*, 1976). In all but one of the inbred strains of mice so far tested it has been possible to show a mating preference based on MHC genotype (Table 1). Variation among strains produces a complex pattern of results, and indicates that genetic background can influence the strength and direction of MHC mate preference. Homozygotes show the strongest mate choice effects as heterozygous individuals tend to display (males) or elicit (females) weak or intermediate responses (Yamazaki *et al.*, 1976). MHC-assortative mating has been consistently observed in one mouse strain, but disassortative mating appears to be the rule (Table 1).

Work on inbred mice shows clearly that mice can make mate choice decisions based on MHC genotype. This information is also used by mice in nature. Using mice derived from wild populations in a seminatural situation (Box 1), Potts *et al.* (1991) found consistent deficiencies in the frequency of MHC homozygous progeny compared to expectation under random mating in a series of study populations. Over all populations there was a highly significant deficit of 27%. After controlling for MHC-related selective fertilization (Wedekind *et al.*, 1996; Rülicke *et al.*, 1998) and abortion (Alberts & Ober, 1993), and having discounted differential mortality in neonates, Potts *et al.* (1991) concluded that most of the observed homozygote deficit was a product of MHC-disassortative mating. Other factors which might be expected to produce a deficiency of MHC homozygotes, such as higher levels of activity (and hence opportunity to mate) or higher fitness in MHC-heterozygous males (suggested by Pomiankowski & Pagel, 1992), were also discounted (Potts *et al.*, 1992a; Potts *et al.*, 1994).

Given the presence of MHC-based mate choice in mice, numerous studies have attempted to detect a similar mechanism in humans. Experimental work on MHC similarity between individuals and odour preferences (Wedekind *et al.*, 1995, Wedekind & Füri, 1997) has suggested that humans can use the MHC in mate choice decisions (but see Hedrick & Loeschcke, 1996). However, convincing evidence that they do so has proved elusive. Homozygote deficiencies at MHC loci have been observed in a number of human populations

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(Alberts & Ober, 1993; Kostyu *et al.*, 1993; Markow *et al.*, 1993) but these could result from balancing selection or patterns of nonrandom mating based on factors other than MHC genotype. Only recently has a study been published in which it has been possible to control for these factors and show a significant association between genotype at the MHC and mate choice in a human population (Ober *et al.*, 1997). Spouses in the Hutterite population - a northern USA and western Canada group isolated by religious beliefs - share MHC haplotypes less often than expected. As in mice, human mating preferences appear to be MHC-disassortative, with no general preference for or avoidance of specific MHC haplotypes (Wedekind *et al.*, 1995; Ober *et al.*, 1997). As the first clear example of a direct association between MHC genotype and actual mate choice outside the genus *Mus*, the results of Ober *et al.* (1997) suggest that the use of the MHC in mate choice decisions may extend across mammals and perhaps all vertebrates.

Studies on mate choice and the MHC in species other than mice and humans are still in their infancy, due in large part to difficulties in routinely typing MHC loci for species in which the MHC has only recently been described. Results have currently been published for two other species, ring-necked pheasants (von Schantz *et al.*, 1996) and Soay sheep (Paterson & Pemberton, 1997). Common to both papers is the use of populations which are subject to long-term intensive study, for which a detailed background knowledge of the ecology (particularly demography) exists. No evidence for MHC-based mate choice was found in the Soay sheep population - see below for possible explanation - but an association between MHC genotype and male ornamentation in ring-necked pheasants strongly suggests that the MHC has a role in mate choice.

The entire field of research on mate choice and the MHC has attracted considerable controversy, (Pomiankowski & Pagel, 1992; Alberts & Ober, 1993; Hughes & Hughes, 1995; Hedrick & Loeschcke, 1996; Gill, 1998). In particular, the reliability of the conclusions from an initial study on MHC genotype and odour preferences in humans (Wedekind *et al.*, 1995) has been severely questioned (Hedrick & Loeschcke, 1996). Moreover, although a second study produced similar findings (Wedekind and Füri, 1997), a lack of repeatability of results from individuals common to both studies must raise futher doubts about the robustness of these findings.

A more general criticism that has been raised is that there has been no demonstration that mate choice is MHC-based and not merely MHC-associated. It may be that mate choice is being made on the basis of genotype at loci which are

Box 1. Experimental designs in studies of mate choice in mice.

1 Yamazaki *et al.* (1976, 1978, 1988); Beauchamp *et al.* (1988)
Only male mate preference was directly tested. Three pairs of MHC-congenic strains were used (BALB and BALB.B; B6 and B6-*H-2*^{k}; B10 and B10.A). Single males were placed in a cage with two receptive females, one of a MHC genotype identical to the male, the other of the MHC-congenic strain. Mate choice was determined by first mating. Preference was assessed at two levels: at the individual level as **consistency of choice** for similar/dissimilar MHC type in successive trials, and as **strain preference** over all trials involving a congenic strain. Inferences about female preference were made by analysis of consistency of choice in trials involving the same female.

To investigate the effects of familial MHC genotype and rearing environment mice from two pairs of MHC-congenic strains were crossed (BALB $\times$ BALB.B and B6-*H-2*^{k} $\times$ B6) to produce progeny which were all heterozygous at the MHC. An F_2 generation was then derived from these individuals and after MHC genotyping only homozygotes were retained postweaning for testing, and in the case of some strains (BALB and BALB.B), for production of a F_3 generation. In addition, a group of BALB mice were bred in complete isolation from mice of other MHC-congenic strains, with a subgroup moved upon weaning to be caged continuously with isolated BALB.B females until testing.

Cross-fostering experiments, where entire litters of one MHC-congenic strain (B6) were fostered to parents of another (B6-*H-2*^{k}) shortly after birth and *vice versa*, were used to examine the effect of early experience on mating preferences.

2 Egid & Brown (1989); Eklund *et al.* (1991); Eklund (1997a,b)
Both male and female choice directly tested. MHC-congenic strains [B10.CHR51 (CHR) and B10.GAA37 (GAA)] or wild house mice were tested. Again an individual was given the opportunity to mate with alternative MHC genotypes, but in this case the two individuals of the same sex were tethered in the opposite end chambers of a three-chambered box. Test individuals were introduced into the centre chamber, but had free access to both end chambers. Mating preference was assessed both by time spent with each MHC type and by first ejaculation, and was reported in terms of strain preference. Cross-fostering experiments were also conducted, but here they involved the reciprocal transfer of single pups between litters of MHC-congenic strains, rather than the transfer of entire litters.

3 Potts *et al.* (1991); Manning *et al.* (1992a)
MHC-based mating and communal nesting patterns in outbred mice in a seminatural situation were examined. Mice derived from wild populations, but bred to carry MHC haplotypes from inbred strains, were held in large outdoor enclosures under frequent behavioural observation, and exposed to normal pathogen loads. A series of nine experimental populations were established in this way, with each disbanded after $\approx$150 progeny had been born. During the life of the population biopsy samples were taken from progeny around the time of weaning, and upon disbanding of each population the remaining progeny (including embryos from pregnant females) were sampled for MHC genotyping.

linked to MHC loci, and that MHC allelic variation *per se* is not important. Such criticism is based on the fact that MHC-congenic mice strains can differ across relatively large parts of the MHC, a chromosomal region which is rich in other genes as well as MHC loci (Klein, 1986). Even the outbred mice used in the experiments of Potts *et al.* (1991) carried MHC haplotypes from inbred lines. Disassortative mating may therefore have been on the basis of strain differences at loci other than class I and class II MHC genes (Hughes & Hughes, 1995). Similarly, high levels of linkage disequilibrium among MHC loci as a result of natural selection (Hedrick, 1994), which maintains haplotypes that differ both at MHC genes and across a range of intervening loci, might account for MHC-disassortative mating in natural populations. Citing unpublished results of further studies on the Hutterites Weitkamp & Ober (1998) have recently suggested that genotypes at non-MHC loci in the MHC region do contribute to MHC haplotype differences among individuals which are important in mate choice.

It has also been suggested that differences in the pattern of nucleotide polymorphism between the antigen binding region (ABR) and non-ABR areas of MHC loci (Hughes & Nei, 1988, 1989) are not explained by sexual selection (Hughes & Hughes, 1995). However, this is not true if it is the binding

Table 1 Summary of results from studies on MHC-based mate choice in inbred strains of mice. References: 1, Yamazaki *et al.* (1976); 2, Yamazaki *et al.* (1978); 3, Yamaguchi *et al.* (1978); 4, Andrews & Boyse (1978); 5, Eklund *et al.* (1991); 6, Egid & Brown (1989)

Strain	Generation	Sex	Strain preference	Consistency of Choice	Reference
BALB	Inbred	M	None/Disassortative[1]	Yes	1
		F	Not tested[3]	No	1
	Inbred	M	Disassortative	Not reported[4]	2
	(Isolated)	F	Not tested	Not reported	2
	F2	M	None/Disassortative[1]	Not reported	2
		F	Not tested	Yes	2
	F3	M	None	Not reported	2
		F	Not tested	Not reported	2
BALB.B	Inbred	M	Assortative	Yes	1
		F	Not tested	No	1
	Inbred	M	Not tested	Not reported	2
	(Isolated)	F	Not tested	Yes	2
	F2	M	Assortative	Not reported	2
		F	Not tested	Not reported	2
	F3	M	Assortative[2]	Not reported	2
		F	Not tested	Not reported	2
BALB.HTG*	Inbred	M	None	Not reported	3
		F	Not tested	Not reported	3
B6	Inbred	M	Disassortative	Yes	1
		F	Not tested	No	1
	F2	M	Disassortative	Not reported	2
		F	Not tested	Not reported	2
B6-*H-2*^{k}	Inbred	M	Disassortative	Yes	1
		F	Not tested	No	1
	F2	M	None	Not reported	2
		F	Not tested	Not reported	2
B6.Tla^{a}	Inbred	M	Assortative	Not reported	4
		F	Not tested	Not reported	4
B10	Inbred	M	Disassortative	No	1
		F	Not tested	No	1
B10.A	Inbred	M	Disassortative	No	1
		F	Not tested	No	1
B10.GAA	Inbred	M	None	Not tested	5
		F	Disassortative	Not tested	6
B10.CHR	Inbred	M	None	Not tested	5
		F	Disassortative	Not tested	6

[1] No strain preference when tested against inbred females, but disassortative when tested against F_2 generation females.
[2] Significantly assortative mating preference when tested with inbred females. Assortative, but not significantly so when tested against F_3 females.
[3] In some experimental designs it was not possible to test all effects.
[4] Result of test not reported.

characteristics of MHC molecules which determine individual odour (and hence mating preference), either directly through binding of volatile molecules or indirectly by controlling an individual's commensal bacteria fauna (Singer *et al.*, 1997; Zavazava & Eggert, 1997).

MHC loci remain prime candidates for involvement in mate choice. The exceptionally high levels of polymorphism at MHC loci provide the variability required for a genetically based recognition system, and plausible hypotheses exist for the mechanisms by which MHC molecules might generate individual odours (Zavazava & Eggert, 1997). Useful though MHC-congenic strains have been in the past, it may be that use of transgenic mice is the only way to unequivocally demonstrate a direct role for MHC loci in mate choice: transgenic techniques allow the generation of highly specific genetic differences among individuals (e.g. single gene differences), so eliminating the influence of other loci as confounding factors.

Do males or females choose?

The relatively weak mate choice in female mice compared to males found in early studies (Table 1; Yamazaki *et al.*, 1976) was a surprising result, as sexual selection theory predicts that in species where females invest more in offspring, females will be the choosier sex. Later work on the same inbred strains (Yamazaki *et al.*, 1978) suggested that females could express a MHC mate preference: there was evidence of consistency of choice in females. In addition, the appearance of strain preference in males in some cases was dependent on the group of females that they were tested against (Table 1). Stronger evidence for female MHC-based mate choice was provided by studies on a different pair of MHC-congenic strains using an experimental design in which both males and females were directly tested for mate choice (Egid & Brown, 1989; Eklund *et al.*, 1991). However, even in those inbred strains which show stronger female than male mate preference, the strength of female choice was labile (see Eklund, 1997a).

While the appearance of stronger mate choice by males may have resulted from the design of early experiments (Box 1), Manning *et al.* (1992b) have suggested that changes in behaviour resulting from the inbreeding process, especially selection against female mate choice, would in fact predict stronger mate choice in males compared to females in inbred strains. On these grounds they have questioned the relevance of using inbred strains in mate choice experiments.

Indeed, in outbred mice females do seem to be the choosier sex. In laboratory-based tests of wild mice against inbred strains (GAA and CHR strains), male mice showed no mate preference (Eklund, 1997b). Relatively few females mated (even when the trial duration was extended from 4 to 12 hours), but females of two rearing groups out of three did spend significantly more time with GAA than CHR males, which was taken to be indicative of mate choice on the basis of MHC genotype. However, variation among the MHC-congenic strains in variables such as size (GAA males tended to be heavier), and a lack of knowledge about the MHC genotype of the wild mice render conclusions from this study tentative.

Laboratory-based mate choice experiments have assessed mate choice on the basis of first mating (Box 1), but wild mice display complex patterns of mating, including multiple matings and extra-pair copulations (Manning *et al.*, 1992b). When this complexity of mating system was allowed to become established under seminatural conditions some interesting patterns emerged (Potts *et al.*, 1991). Patterns of female settlement, controlled by males, were non-random with respect to the MHC, and within-territory matings accounted for approximately one quarter of the observed MHC homozygous deficit (Potts *et al.*, 1992b). It appeared that males were exercising MHC-based choice in this situation as well as in the laboratory. However, analysis of genetic data combined with behavioural observations revealed that extraterritorial matings by females were the main cause of the observed MHC homozygote deficiency. Females often mated with males other than the male whose territory contained her nestbox, and in these extraterritorial matings females tended to choose males which were more MHC-dissimilar than their territorial male.

Evidence for a less direct association between MHC genotype and female mate choice comes from ring-necked pheasants (von Schantz *et al.*, 1996). In this species mate choice by females has been shown to be based on a variety of male secondary sexual characters, including spur length. Von Schantz *et al.* (1996) have shown that spur length is also associated with MHC genotype. This result supports the Hamilton & Zuk (1982) hypothesis that the quality of male ornamentation is condition dependent, and is associated with an individual's genotype at loci involved in the immune response and an ability to resist pathogens.

Self-reference or learning?

In inbred mice strains the direction of individual MHC-based mate choice (i.e. assortative vs. disassortative) was often found to be counter to the strain preference (Yamazaki *et al.*, 1976). Genotype does not therefore seem to be the absolute determinant of MHC-based mating preference, and it was suggested that environment might have a role. However, further studies on the influence of environment on MHC-based mate choice produced conflicting results (Yamazaki *et al.*, 1978; see Box 1 for details of these experiments). Rearing mice to weaning in isolation from other MHC-congenic strains, so that they had experience of only one MHC genotype, could induce mating preferences not seen in non-isolated individuals of the same strain and generation. However, it was also found that while inbred and F_3 groups (which had homozygous familial MHC genotypes) showed no MHC-based mating preference, F_2 males (which had preweaning experience of other MHC genotypes as they were progeny of heterozygous parents) did show strain preference.

The suggestion that experience in early life, particularly the familial environment, could affect subsequent MHC-based mating preference was confirmed by cross-fostering experiments (Beauchamp *et al.*, 1988; Yamazaki *et al.*, 1988). MHC mating preferences were reversed in males cross-fostered soon after birth to MHC-dissimilar parents, but remained disassortative in mice fostered to MHC-similar parents. Mate choice appeared not to be based on reference to self MHC genotype but was learned from parental MHC genotype. However, preliminary results of cross-fostering experiments with females suggested that, unlike males, the parental MHC

genotype had no effect on female mate choice (Beauchamp *et al.*, 1988). Results of cross-fostering experiments with GAA and CHR strains were equivocal (Eklund, 1997a), mostly because in these experiments unfostered, control-group mice did not show any MHC-based mating preference. However, one statistically significant result was obtained. GAA females cross-fostered to a CHR family mated preferentially with GAA males, again indicating that early life experience can influence MHC-based mate choice decisions, but in females in this case.

An important result of Ober *et al.* (1997) was that in human couples with a shared MHC haplotype, the matching haplotype was maternally derived less often than paternally derived, and less often than expected under random mating given the genealogy of the samples. In other words, an individual's choice was biased towards avoiding a partner with a MHC haplotype similar to that found in their mother, suggesting some form of maternal imprinting, perhaps in early life - consistent with the previously described results of studies on preweaning experience in mice (Beauchamp & Yamazaki, 1997).

Effect of hormonal status on MHC preferences

In a companion study to the experiments of Potts *et al.* (1991) on mate choice, Manning *et al.* (1992a) examined the pattern of communal nesting and rearing of young by female mice. Here, MHC-similar individuals were preferred as nest partners. That this shift in MHC genotype preference reflected hormonal status was suggested by Y-maze tests where (inbred) females in oestrus spent significantly more time near the odour of MHC-dissimilar males than MHC-similar males, while females in metoestrus displayed no preference (Egid & Brown, 1989).

In humans a negative correlation between degree of MHC similarity and level of odour preference has been reported in both men and women (Wedekind *et al.*, 1995; Wedekind & Füri, 1997). However, for women taking oral contraceptives, the correlation between MHC similarity and odour preference was positive, although it was not statistically significant in the second study (Wedekind & Füri, 1997). Hormonal status appears to modulate MHC-based preferences in humans as well as mice.

Although these results might not directly relate to the role of the MHC in mate choice, as it may be argued that females are not likely to be choosing a mate when in metoestrus or when under the influence of hormonal contraceptives, they are interesting in that they show that MHC genotype preferences are crucially dependent on the context in which they are expressed.

Social structure, mating system, and genome structure

Variation in social structure and mating system may have an influence on the importance of the MHC in mate choice decisions, and on the detection of any effect. For example, early population-level studies on HLA (the human MHC) and mate choice repeatedly found no evidence of disassortative mating which could be attributed to the effect of HLA genotype alone (Pollack *et al.*, 1982; Rosenberg *et al.*, 1983; Jin *et al.*, 1995). However, the high level of polymorphism at HLA loci in modern human populations (Parham & Ohta, 1996) creates a situation where few individuals share MHC haplotypes, and tests of MHC-based mate choice in humans were often compromised by the small sample sizes available for matings between MHC-similar individuals (Jin *et al.*, 1995). Additionally, non-random mating on the basis of other factors may confound any direct effect of MHC genotype on human mate choice. For instance, matings between close relatives are often proscribed or discouraged, thereby reducing the number of MHC-similar matings (Ober *et al.*, 1997). Conversely, subdivision by ethnic, racial and cultural boundaries, with differences in MHC haplotype frequencies among groups, may increase the level of mating among MHC-similar individuals (Rosenberg *et al.*, 1983). Two recent studies have attempted to circumvent these problems by studying small, inbred and ethnically homogeneous populations, with (consequently) relatively low levels of MHC diversity (Hedrick & Black, 1997; Ober *et al.*, 1997).

The results of the two studies initially appear to conflict: Hedrick & Black (1997) found no evidence of HLA-disassortative mating in 11 tribes of South Amerindians from the lower Amazon basin, while Ober *et al.* (1997) detected HLA-disassortative mating in the Hutterites. However, of the two studies, that of Ober *et al.* (1997) was considerably more comprehensive with a sample size of 411 couples typed at both class I (HLA-A, -B, -C) and class II (HLA-DQ and -DR) loci, compared to 195 couples typed only at HLA-A and -B considered by Hedrick & Black (1997) — an important consideration given the demonstrated increase in power gained through analysis of haplotype differences over many loci (Weitkamp & Ober, 1998). Ober *et al.* (1997) also managed to accommodate the effect of non-random mating due to Hutterite cultural practices by using an exact genealogy of the sampled individuals to generate expected distributions of haplotype frequencies by computer simulation.

It may be that detailed and large-scale studies such as that of Ober *et al.* (1997) are required to detect the relatively weak effects of HLA genotype on odour/mate preference reported by Wedekind *et al.* (1995) (Hedrick & Loeschcke, 1996; Hedrick & Black, 1997), or that the effect is not found in many human societies, either because other (cultural) factors are more important or due to the low likelihood of encountering potential mates with a similar MHC genotype (Hedrick & Black, 1997; Beauchamp & Yamazaki, 1997; Ober *et al.*, 1997). Intriguingly, however, while Hedrick & Black (1997) concede the lack of power in their study to detect weak effects, they note that their observations (although statistically non-significant) were the reverse of that expected under disassortative mating.

Paterson & Pemberton (1997) have used demographic information and paternity analysis available for the Soay sheep population of St. Kilda (an island archipelago off the north-west coast of Scotland) to examine mating patterns in relation to MHC type. Using microsatellite loci as markers for MHC haplotype, they found no evidence for non-random mating with respect to the MHC, even after careful consideration of factors which might prevent detection of a weak effect (such as the power of their analysis). They suggested that as male-male competition appears to be the primary mechanism for determining mating success in Soay sheep, females have little opportunity to choose mates on any basis, and MHC-based mate choice might therefore be expected to

be weak in this species. In contrast, as mentioned above, in ring-necked pheasants where female mate choice is strong, the MHC does appear to have a role (von Schantz *et al.*, 1996).

Work on *Mus* and humans continues to improve our understanding of MHC-based mate choice, but if this system is to be shown to have more general relevance the most exciting prospects for this field lie in further studies on a wider range of vertebrate species. In particular, species in which there is little or no social context for kin recognition but a high probability of inbreeding (e.g. some bird, reptile and fish species which undertake long-distance migrations in early life but show strong philopatry to the natal site), may have a greater requirement for a genetically based kin recognition system than the relatively social mammals examined so far. In this respect, it is interesting to note recent reports that MHC loci do not always exist in a single tightly linked cluster as they do in mammals, but can be found in two (e.g. chicken; Miller *et al.*, 1994) or multiple (e.g. zebrafish: Bingulac-popovic *et al.*, 1997) clusters. A wider distribution of MHC genes provides a greater number of independent 'matching loci' (Grafen, 1990) for estimating relatedness than the mammalian configuration, and suggests that such taxa may provide a fruitful area of future research in this field.

Consequences of MHC-based mate choice

Under certain circumstances the strength of female mate choice observed in experiments on mice has the potential to maintain high levels of polymorphism, and to generate homozygote deficiencies and linkage disequilibrium, and these are all characteristics of the genetics of the MHC in natural populations (Potts *et al.*, 1991; Hedrick, 1992). MHC-disassortative mating may be a mechanism to increase heterozygosity specifically at the MHC, or to prevent inbreeding in general — objectives which are entirely compatible (Potts *et al.*, 1994). In mammals, MHC-based mate choice seems to have some dramatic and immediate consequences. Fertilization efficiency appears dependent on the specific combination of MHC alleles in egg and sperm, and may be condition dependent (Wedekind *et al.*, 1996; Rülicke *et al.*, 1998). Furthermore, MHC-similar couples experience higher levels of spontaneous abortion (Alberts & Ober, 1993), probably due to some MHC-dependent maternal-foetal interaction (Gill, 1994; Black & Hedrick, 1997). Whether or not other vertebrate species show similar reproductive phenomena associated with the MHC remains to be seen.

The dual function of MHC loci in kin recognition and disease resistance suggests that MHC genotype might be used in two ways in mate choice — signalling relatedness through distinctive individual odours, and signalling immune response genotype and immunocompetence either through odour or costly secondary sexual characters. Evidence that both signalling systems have a role in nature is beginning to accumulate, but as mate choice studies become more refined and yet wide-ranging, the parallel use of MHC analysis is likely to yield new insight on the genetic basis of mate choice.

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References

ALBERTS, S. C. AND OBER, C. 1993. Genetic variability of the MHC: a review of non-pathogen-mediated selective mechanisms. *Yb. Phys. Anthropol.*, **36**, 71–89.

ANDREWS, P. W. AND BOYSE, E. A. 1978. Mapping of an *H-2*-linked gene that influences mating preference in mice. *Immunogenet.*, **6**, 265–268.

BEAUCHAMP, G. K. AND YAMAZAKI, K. 1997. HLA and mate selection in humans: commentary. *Am. J. Hum. Genet.*, **61**, 494–496.

BEAUCHAMP, G. K., YAMAZAKI, K., BARD, J. AND BOYSE, E. A. 1988. Preweaning experience in the control of mating preferences by genes in the major histocompatibility complex of the mouse. *Behav. Genet.*, **18**, 537–547.

BINGULAC-POPOVIC, J., FIGUEROA, F., SATO, A., TALBOT, W. S., JOHNSON, S. L., GATES, M. *ET AL*. 1997. Mapping of *Mhc* class I and class II regions to different linkage groups in the zebrafish, *Danio rerio*. *Immunogenetics*, **46**, 129–134.

BLACK, F. L. AND HEDRICK, P. W. 1997. Strong balancing selection at HLA loci: evidence from segregation in South Amerindian families. *Proc. Natl. Acad. Sci., U.S.A.*, **94**, 12,452–12,456.

BROWN, J. L. 1997. A theory of mate choice based on heterozygosity. *Behav. Ecol..*, **8**, 60–65.

BROWN, J. L. AND EKLUND, A. 1994. Kin recognition and the major histocompatibility complex: an integrative review. *Am. Nat.*, **143**, 435–461.

EGID, K. AND BROWN, J. L. 1989. The major histocompatibility complex and female mating preferences in mice. *Anim. Behav.*, **38**, 548–550.

EKLUND, A. 1997a. The effect of early experience on MHC-based mate preferences in two B10. W Strains of mice. *Behav. Genet.*, **27**, 223–229.

EKLUND, A. 1997b. The major histocompatibility complex and mating preferences in wild house mice. *Behav. Ecol..*, **8**, 630–634.

EKLUND, A., EGID, K. AND BROWN, J. L. 1991. The major histocompatibility complex and mating preferences of male mice. *Anim. Behav.*, **42**, 693–694.

FOLSTAD, I. AND KARTER, A. J. 1992. Parasites, bright males, and the immunocompetence handicap. *Am. Nat.*, **139**, 603–622.

GILL, T. J. III 1994. Reproductive Immunology and Immunogenetics. In: Knobil, E. & Neill, J. D. (eds) *The Physiology of Reproduction*, pp. 783–812. Raven Press, Ltd., New York.

GILL, T. J. III 1998. HLA and mate choice. *Am. J. Hum. Genet.*, **62**, 985–986.

GRAFEN, A. 1990. Do animals really recognise kin? *Anim. Behav.*, **39**, 42–54.

HAMILTON, W. D. 1964. The genetical evolution of social behaviour. *I. J. Theoret. Biol.*, **7**, 1–16.

HAMILTON, W. D. AND ZUK, M. 1982. Heritable true fitness and bright birds: a role for parasites. *Science*, **218**, 384–387.

HEDRICK, P. W. 1992. Female choice and variation in the major histocompatibility complex. *Genetics*, **132**, 575–581.

HEDRICK, P. W. 1994. Evolutionary genetics of the major histocompatibility complex. *Am. Nat.*, **143**, 945–964.

HEDRICK, P. W. AND BLACK, F. L. 1997. HLA and mate selection: no evidence in South Amerindians. *Am. J. Hum. Genet.*, **61**, 505–511.

HEDRICK, P. W. AND LOESCHCKE, V. 1996. MHC and mate selection in humans? *Trends Ecol.. Evol.*, **11**, 24.

HUGHES, A. L. AND HUGHES, M. K. 1995. Natural selection on the peptide-binding regions of major histocompatibility complex molecules. *Immunogenet.*, **42**, 233–243.

HUGHES, A. L. AND NEI, M. 1988. Pattern of nucleotide substitution at major histocompatibility complex class I loci reveals overdominant selection. *Nature*, **335**, 167–170.

HUGHES, A. L. AND NEI, M. 1989. Nucleotide substitution at major histocompatibility complex class II loci: evidence for overdominant selection. *Proc. Natl. Acad. Sci., U.S.A.*, **86**, 958–962.

JIN, K., SPEED, T. P. AND THOMSON, G. 1995. Tests of random mating for a highly polymorphic locus: application to HLA data. *Biometrics*, **51**, 1064–1076.

KLEIN, J. 1986. *Natural History of the Major Histocompatibility Complex*. Wiley, New York.

KOSTYU, D. A., DAWSON, D. V., ELIAS, S. AND OBER, C. 1993. Deficit of HLA homozygotes in a caucasian isolate. *Hum. Immunol.*, **37**, 135–142.

MANNING, C. J., POTTS, W. K. AND WAKELAND, E. K. 1992a. Communal nesting patterns in mice implicate MHC genes in kin recognition. *Nature*, **360**, 581–583.

MANNING, C. J., POTTS, W. K., WAKELAND, E. K. AND DEWSBURY, D. A. 1992b. What's wrong with MHC mate choice experiments? In: Doty, R. L. & Müller-Schwarze, D. (eds) *Chemical Signals in Vertebrates VI*, pp. 229–235. Plenum Press, New York.

MARKOW, T., HEDRICK, P. W., ZUERLEIN, K., DANILOVS, J., MARTIN, J., VYVIAL, T. AND ARMSTRONG, C. 1993. HLA polymorphism in the Havasupai: evidence for balancing selection. *Am. J. Hum. Genet.*, **53**, 943–952.

MILLER, M. M., GOTO, R., BERNOT, A., ZOOROB, R., AUFFRAY, C., BUMSTEAD, N. AND BRILES, W. E. 1994. Two Mhc class I and two Mhc class II genes map to the chicken Rfp-Y system outside the B complex. *Proc. Natl. Acad. Sci., USA*, **91**, 4397–4401.

OBER, C., WEITKAMP, L. R., COX, N., DYTCH, H., KOSTYU, D. AND ELIAS, S. 1997. HLA and mate choice in humans. *Am. J. Hum. Genet.*, **61**, 497–504.

PARHAM, P. AND OHTA, T. 1996. Population biology of antigen presentation by MHC Class I molecules. *Science*, **272**, 67–74.

PATERSON, S. AND PEMBERTON, J. M. 1997. No evidence for major histocompatibility complex-dependent mating patterns in a free-living ruminant population. *Proc. R. Soc. Lond. B*, **264**, 1813–1819.

POLLACK, M. S., WYSOCKI, C. J., BEAUCHAMP, G. K., BRAUN, D., CALLAWAY, C. AND DUPONT, B. 1982. Absence of *HLA* association or linkage for variations in sensitivity to the odor of androstenone. *Immunogenet.*, **15**, 579–589.

POMIANKOWSKI, A. AND PAGEL, M. 1992. Sexual selection and MHC genes. *Nature*, **356**, 293–294.

POTTS, W. K., MANNING, C. J. AND WAKELAND, E. K. 1991. Mating patterns in seminatural populations of mice influenced by MHC genotype. *Nature*, **352**, 619–621.

POTTS, W. K., MANNING, C. J. AND WAKELAND, E. K. 1992a. Sexual selection and MHC genes: reply to Pomiankowski and Pagel. *Nature*, **356**, 294.

POTTS, W. K., MANNING, C. J. AND WAKELAND, E. K. 1992b. MHC-based mating preferences in *Mus* operate through both settlement patterns and female controlled extra-territorial matings. In: Doty, R. L. & Müller-Schwarze, D. (eds) *Chemical Signals in Vertebrates VI*, pp. 183–187. Plenum Press, New York.

POTTS, W. K., MANNING, C. J. AND WAKELAND, E. K. 1994. The role of infectious disease, inbreeding and mating preferences in maintaining MHC genetic diversity: an experimental test. *Phil. Trans. R. Soc. Lond. B*, **346**, 369–378.

ROSENBERG, L. T., COOPERMAN, D. AND PAYNE, R. 1983. HLA and mate selection. *Immunogenet.*, **17**, 89–93.

RÜLICKE, T., CHAPUISAT, M., HOMBERGER, F. R., MACAS, E. AND WEDEKIND, C. 1998. MHC-genotype of progeny influenced by parental infection. *Proc. R. Soc. Lond. B*, **265**, 711–716.

SCOFIELD, V. L., SCLUMPBERGER, J. M., WEST, L. A. AND WEISSMAN, I. L. 1982. Protochordate allorecognition is controlled by a MHC-like gene system. *Nature*, **295**, 499–502.

SINGER, A. G., BEAUCHAMP, G. K. AND YAMAZAKI, K. 1997. Volatile signals of the major histocompatibility complex in male mouse urine. *Proc. Natl. Acad. Sci. USA*, **94**, 2210–2214.

THOMAS, L. 1975. Symbiosis as an immunological problem. The immune system and infectious disease. In: Neter, E. & Milgrom, F. (eds) *Fourth International Convocation of Immunology*, pp. 2–11. S. Karger, New York.

VON SCHANTZ, T., WITTZELL, H., GÖRANSSON, G., GRAHN, M. AND PERSSON, K. 1996. MHC genotype and male ornamentation: genetic evidence for the Hamilton-Zuk model. *Proc. R. Soc. Lond. B*, **263**, 265–271.

WEDEKIND, C. 1994. Mate choice and maternal selection for specific parasite resistances before, during and after fertilization. *Phil. Trans. R. Soc. Lond. B*, **346**, 303–311.

WEDEKIND, C. AND FÜRI, S. 1997. Body odour preferences in men and women: do they aim for specific MHC combinations or simply heterozygosity? *Proc. R. Soc. Lond. B*, **264**, 1471–1479.

WEDEKIND, C., CHAPUISAT, M., MACAS, E. AND RÜLICKE, T. 1996. Non-random fertilization in mice correlates with the MHC and something else. *Heredity*, **77**, 400–409.

WEDEKIND, C., SEEBECK, T., BETTENS, F. AND PAEPKE, A. J. 1995. MHC-dependent mate preferences in humans. *Proc. R. Soc. Lond. B*, **260**, 245–249.

WEITKAMP, L. R. AND OBER, C. 1998. HLA and mate choice: reply to Gill. *Am. J. Hum. Genet.*, **62**, 986–987.

YAMAGUCHI, M., YAMAZAKI, K. AND BOYSE, E. A. 1978. Mating preference tests with the recombinant congenic strain BALB. HTG*. *Immunogenet.*, **6**, 261–264.

YAMAZAKI, K., BEAUCHAMP, G. K., KUPNIEWSKI, D., BARD, J., THOMAS, L. AND BOYSE, E. A. 1988. Familial imprinting determines H-2 selective mating preferences. *Science*, **240**, 1331–1332.

YAMAZAKI, K., BOYSE, E. A., MIKÉ, V., THALER, H. T., MATHIESON, B. J., ABBOTT, J. *ET AL*. 1976. Control of mating preferences in mice by genes in the major histocompatibility complex. *J. Exp. Med.*, **144**, 1324–1335.

YAMAZAKI, K., YAMAGUCHI, M., ANDREWS, P. W., PEAKE, B. AND BOYSE, E. A. 1978. Mating preferences of F_2 segregants of crosses between MHC-congenic mouse strains. *Immunogenet.*, **6**, 253–259.

ZAVAZAVA, N. AND EGGERT, F. 1997. MHC and behaviour. *Immunol. Today*, **18**, 8–10.