# Scent, Mate Choice and Genetic Heterozygosity

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**Abstract** Females of many species choose to mate with relatively unrelated males in order to ensure outbred, heterozygous offspring. There is some evidence to suggest that the MHC is involved in mate choice decisions, either because MHC heterozygous offspring are more resistant to disease, or because the highly detectable odours associated with this region allow it to act as a marker of general inbreeding. To determine which role the MHC plays it is necessary to disentangle this region from the genetic background, a requirement which has generally proven difficult to achieve. We argue that the emphasis on MHC's role in mate choice has resulted in other potential markers of inbreeding being neglected, and discuss the evidence for MHC disassortative mating, the interaction with genetic background, and a possible role for alternative markers of inbreeding.

## 1 Introduction

Female animals generally favour some males over others as potential mating partners, and those allowed to mate with their preferred male often have greater fitness than when mated with a non-preferred alternative (Drickamer, Gowaty and Holmes 2000; Persaud and Galef 2005). One way in which choosy females may improve their fitness is by selecting males that will produce genetically superior offspring (see Byers and Waits 2006 for a recent example). These males may either provide good genes that improve offspring fitness traits, or they may be relatively more compatible with the choosing female's genotype (Zeh and Zeh 1996; Brown 1997; Tregenza and Wedell 2000; Mays and Hill 2004). While good genes effects are additive and broadly speaking are expressed independently of the maternal genome, compatibility effects are nonadditive and are determined by the interaction between the parental genotypes (Zeh and Zeh 1996). This leads to a key difference between the good genes and compatibility explanations for female choice: while females will usually agree about which males carry good genes, the most compatible male

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will vary depending on the genotype of the choosing female. Parental genetic compatibility often improves fitness by increasing the genetic heterozygosity of offspring (but see also Zeh and Zeh 1996), a mechanism which is most familiar from the special case of inbreeding avoidance. In fact, preference for compatible partners and avoidance of inbreeding overlap considerably, since close relatives will often be genetically incompatible (Brown 1997). Here we discuss the detrimental effects of incompatibility, particularly inbreeding, and consider the behavioural mechanisms and signalling systems which may have evolved to avoid these costs.

## 2 Genetic Compatibility and Inbreeding Avoidance

The main consequence of mating between genetically dissimilar partners is increased heterozygosity of offspring, which may itself be the primary advantage of sexual reproduction (Brown 1997). Genetic heterozygosity can influence fitness via two main mechanisms: either because it avoids unmasking any deleterious recessive alleles carried by either parent (the dominance hypothesis), or because heterozygotes are inherently superior to homozygotes (overdominance: Charlesworth and Charlesworth 1987). Whatever the underlying mechanism, homozygosity is frequently detrimental to reproductive success, having been shown to reduce hatching success or embryo survival, litter size, and survival of offspring in captive studies (e.g. Ralls, Ballou and Templeton 1988; Keane, Creel and Waser 1996; e.g. Pusey and Wolf 1996; Bixler and Tang-Martinez 2006). Accumulating data support the idea that genetic similarity among mating partners also has negative effects on offspring number and survival in the wild (Stockley, Searle, Macdonald and Jones 1993; Coltman, Bowen and Wright 1998; Crnokrak and Roff 1999; Keller and Waller 2002; Slate and Pemberton 2002). The detrimental effects of inbreeding may continue into adulthood, with inbred individuals suffering a reduction in survival (Jiménez, Hughes, Alaks, Graham and Lacy 1994; Keller, Arcese, Smith, Hochachka and Stearns 1994; Coltman, Pilkington, Smith and Pemberton 1999), ability to hold territories (Meagher, Penn and Potts 2000), and reproductive success (Keller 1998; Slate, Kruuk, Marshall, Pemberton and Clutton-Brock 2000; Seddon, Amos, Mulder and Tobias 2004).

Given these costs, we would expect the evolution of behavioural mechanisms to reduce the risk of inbreeding. In some species, this is achieved by sex-biased dispersal: members of one sex predominantly leave the natal range and hence minimize the likelihood of encountering relatives as mates (Pusey 1987; Pusey and Wolf 1996). By contrast, species without sex-biased dispersal, and particularly those with aggregated population structures, are likely to risk mating with close relatives. Such species should benefit from kin recognition systems that allow them to recognize and avoid close kin as mates. Active mate preference for non-kin does indeed appear to be widespread, and has been demonstrated in numerous groups including insects (Simmons 1991), marsupials (Parrott, Ward and Temple-Smith 2007), rodents (Krackow and Matuschak 1991; Keane et al. 1996;

Ryan and Lacy 2003), and primates (Smith 1995; Soltis, Mitsunaga, Shimizu, Yanagihara and Nozaki 1999). This preference can be very strongly expressed: females of some species choose not to mate at all when no unrelated males are available (woodpeckers: Koenig, Stanback and Haydock 1999; mole rats: Cooney and Bennett 2000; meerkats: O'Riain, Bennett, Brotherton, McIlrath and Clutton-Brock 2000).

## 3 The Role of MHC in Mate Choice

Behavioural avoidance of inbreeding requires a mechanism for reliably identifying kin, a signal which should be easily detectable, polymorphic and heritable. Much work in vertebrates has focussed on the role of the major histocompatibility complex (MHC), a highly polymorphic region of the vertebrate genome which is associated with specific odours in a range of species. Numerous studies on rodents have demonstrated their ability to discriminate odours associated with the MHC (Yamaguchi, Yamazaki, Beauchamp, Bard, Thomas and Boyse 1981; Yamazaki, Beauchamp, Bard, Thomas and Boyse 1982), including odour changes resulting from only single amino-acid substitutions (Yamazaki, Beauchamp, Egorov, Bard, Thomas and Boyse 1983), although not all differences are detectable (Carroll, Penn and Potts 2002), Sensitivity to MHC-associated odours has also been suggested for other species including sticklebacks (Reusch, Häberli, Aeschlimann and Milinski 2001), salmonids (Olsén, Grahn, Lohm and Langefors 1998), lizards (Olsson, Madsen, Nordby, Wapstra, Ujvari and Wittsell 2003), rats (Schellinck, Slotnick and Brown 1997) and humans (Wedekind, Seebeck, Bettens and Paepke 1995; Thornhill, Gangestad, Miller, Scheyd, McCullough and Franklin 2003). Although many experiments have focussed simply on discriminability of MHC odours, there is also some evidence that these odours affect mate choice in MHC congenic laboratory mouse strains. In some highly inbred pairs of strains that are genetically identical to one another except at MHC, members of both sexes prefer to mate with partners with a different MHC type to self (Yamazaki, Boyse, Miké, Thaler, Mathieson, Abbott, Boyse, Zayas and Thomas 1976; Egid and Brown 1989). The high degree of polymorphism at MHC, together with the observation that this is associated with easily discriminable odours, and evidence for an effect of MHC on mate choice, have led to the suggestion that the MHC may provide a general mechanism of individual (e.g. Brennan and Kendrick 2006) and kin (e.g. Brown and Eklund 1994) recognition across vertebrates used in the context of mate choice. Recent physiological work has highlighted direct detection of MHC peptides as a possible mechanism by demonstrating that receptors capable of detecting MHC peptides exist in the main olfactory epithelium (Spehr, Kelliher, Li, Boehm, Leinders-Zufall and Zufall 2006) and vomeronasal organ (Leinders-Zufall, Brennan, Widmayer, Chandramani, Maul-Pavicic, Jager, Li, Breer, Zufall and Boehm 2004).

It is frequently suggested that animals choose mating partners with complementary MHC type to self because of the resulting increase in offspring genetic

heterozygosity specifically at this region (Jordan and Bruford 1998; Tregenza and Wedell 2000; Milinski 2006). As the primary role of the MHC is in the adaptive immune system, relatively MHC heterozygous offspring should experience improved pathogen resistance as a result of their ability to recognize a greater range of foreign peptides (Penn, Damjanovich and Potts 2002). This mechanism of responding to an unpredictable disease environment is hypothesised to be a major force in maintaining the MHC's extraordinary levels of polymorphism (Doherty and Zinkernagel 1975; Hughes and Nei 1988). However the expected relationship between MHC heterozygosity and adaptive immune performance has received mixed support. Some studies have supported the assumption of a link between MHC diversity and fitness, reporting greater resistance (Penn et al. 2002), lower pathogen loads (Wegner, Kalbe, Kurtz, Reusch and Milinski 2003; Kurtz, Kalbe, Aeschlimann, Häberli, Wegner, Reusch and Milinski 2004), and higher survival (Westerdahl, Waldenström, Hansson, Hasselquist, Von Schantz and Bensch 2005) at high levels of heterozygosity. Others have failed to find evidence that MHC heterozygosity influences immunity (Paterson, Wilson and Pemberton 1998; Langefors, Lohm, Grahn, Andersen and von Schantz 2001; Wedekind, Walker and Little 2006), or have found the opposite effect. For example, mice heterozygous for MHC performed less well than the homozygote mean when infected with malaria (Wedekind, Walker and Little 2005). Much of the evidence for a link between MHC heterozygosity and ability to combat disease comes from correlational studies, which are generally hampered by the strong link between MHC and background genetic diversity. Failing to control for this correlation means that observed effects could be due simply to genome-wide heterozygosity rather than to the specific effects of MHC (Penn et al. 2002). Indeed, a recent study on wild fish populations found background genetic heterozygosity to be significantly associated with reduced parasite load, while MHC diversity was not (Rauch, Kalbe and Reusch 2006). This link to background genetic diversity has an influence on other aspects MHC's role, as we discuss further below.

## 4 The Confounding Influence of Genetic Background

In natural populations, the level of MHC sharing between a given pair of individuals is normally correlated with their overall similarity across the whole of the genome. This link could enable animals to use the highly variable and detectable MHC to act as a marker of overall genetic relatedness. Whereas the evidence for MHC homozygosity remains ambiguous, inbreeding can have devastating fitness consequences. Given the costs of mating with close kin, the primary role of MHC in mate choice might be to facilitate avoidance of inbreeding more generally, rather than at the MHC itself (Potts, Manning and Wakeland 1994). High levels of MHC polymorphism ensure that individuals in a normal outbreeding population are likely to share a large proportion of their MHC only with very close relatives; disassortative mating would provide the substantial benefits of inbreeding avoidance, while simultaneously ensuring genetic diversity at the MHC.

Whether the role of MHC in mate choice is related specifically to its involvement in immune defence, or because this region is a reliable signal for overall genetic similarity, the failure of most studies to separate the effects of MHC and genetic background means that any observed effect of MHC could be an artefact of experimental design. Much of the evidence for the role of MHC in mate choice comes from studies demonstrating a deficit of MHC homozygotes in natural (e.g. Landry, Garant, Duchesne and Bernatchez 2001) or artificial (e.g. Potts, Manning and Wakeland 1991) populations, an observation consistent with disassortative mating at MHC. However, because MHC homozygotes are most likely to result from matings between close kin, underproduction of these individuals could be a by-product of general inbreeding avoidance rather than a direct consequence of MHC-based disassortative mating. Assuming that inbreeding avoidance is generally important, the signal used to assess and reject genetically similar mates could be encoded in genes completely unrelated to MHC, with the intrinsic correlation between MHC and the rest of the genome ensuring that MHC homozygotes are rare in normally outbreeding populations. It is only possible to assess whether MHC is important for mate choice by disentangling this from the rest of the genome, something most studies have so far been unable to achieve. Attempts to separate MHC and background generally use laboratory-derived strains, and despite their widespread acceptance in the literature, the results obtained by this method have generally been ambiguous or contradictory. For example, the early studies of Yamazaki et al. (1976; 1978) are usually cited in support of MHC disassortative mating, but these studies also found consistent MHC assortative mating in one strain, and assortative mating has also been reported in another laboratory strain (Andrews and Boyse 1978). A more fundamental limitation in experiments controlling for background genes arises from the tendency to use pairs of highly inbred strains differing only at MHC: it is perhaps unsurprising that, given no other source of genetic variation, females sometimes choose males which differ from them at the only variable loci. These experiments have not adequately tested whether females will respond to *any* variable genetic region against a uniform background. However, evidence from more naturalistic studies involving wild animals is limited by the general failure to control adequately for the correlation between background genetic heterozygosity (or other genetic markers) and MHC. For example, overall genetic relatedness in wild populations is often quantified by counting the number of shared markers at microsatellite loci. This method requires examination of relatively large number of loci to minimize misclassification errors (Blouin, Parsons, Lacaille and Lotz 1996), but many studies actually use very few markers (e.g. 5 in the case of Landry et al. 2001). Other workers have attempted to get around these problems by producing semi-natural populations from captive-bred stock with known genotypes. Potts et al. (1991) tested reproductive success in relation to MHC matching using mice partly derived from wild stock. However in these animals 50% of the genome (including the MHC) originated from highly inbred strains and, because individual parentage could not be assigned, it was not possible to assess whether the deficit in MHC homozygotes found in this study was due to the use of non-MHC signals used to avoid inbreeding.

## 5 Alternative Signals in Inbreeding Avoidance

The almost universal acceptance of MHC as a significant factor in vertebrate mate choice (Jordan and Bruford 1998; Penn 2002; see reviews in: Bernatchez and Landry 2003; Brennan and Kendrick 2006; Milinski 2006), despite inconsistent results and the failure to control adequately for background genes, has resulted in a deficit of research on other markers that might be used to avoid inbreeding. House mice, *Mus musculus domesticus,* have evolved a species-specific polygenic and highly polymorphic gene complex coding for major urinary proteins (MUPs), which are excreted in large quantities in the urine and form a substantial component of this species' scent signals. MUPs are known to play a key role in self-nonself recognition (Hurst, Payne, Nevison, Marie, Humphries, Robertson, Cavaggioni and Beynon 2001; Hurst, Thom, Nevison, Humphries and Beynon 2005) and are used by females to identify individual males from their competitive scent marks (Cheetham, Thom, Jury, Ollier, Beynon and Hurst 2007). MUPs have all the characteristics that make the MHC so intuitively appealing as a marker of kinship, including coding by a complex of tightly linked genes that are inherited together as a haplotype. However MUPs differ from MHC in being produced in large quantities in the liver and excreted at high concentration in urine (Humphries, Robertson, Beynon and Hurst 1999; Beynon and Hurst 2003) before being deliberately deposited extensively in the environment via scent marking. This makes them a widespread and easily detectable signal linked to genome-wide genetic heterozygosity. If mice benefit from avoiding inbreeding, as they clearly appear to (e.g. Meagher et al. 2000), we would expect them to mate disassortatively with respect to MUP in order to avoid mating with close kin, leading inevitably to a parallel reduction in homozygosity at MHC. However if the fitness benefits derived from heterozygosity specifically at the MHC are of greater importance than inbreeding avoidance, MHC odours should be used in preference. MUPs thus provide an ideal control system for identifying experimentally the MHC's role in mate choice, since they provide an equivalent polymorphic, polygenic signal closely linked to background genetic heterozygosity but with no implications for immune function. We are taking advantage of this system and breeding wild-derived populations of mice in which the relative contributions of different genetic components are controlled, allowing us to test for the first time the independent contributions to mate choice of MUP, MHC, and overall relatedness. Allowing these animals to breed in semi-natural enclosures has demonstrated that mice use MUP sharing to avoid mating with close kin. Indeed, the deficit in mating with mice of the same MUP type is sufficient to explain entirely the observed level of inbreeding avoidance, with MHC sharing having no detectable influence on mate choice (Sherborne, Thom, Paterson, Jury, Ollier, Stockley, Beynon and Hurst 2007). Previous studies have been unable to control these three components independently, leaving open the possibility that previously observed deficits in MHC homozygotes in freely-breeding populations of mice could result from the avoidance of mates with the same MUP type. Work on laboratory strains has not investigated the role of MUPs in inbreeding avoidance, probably because

variability in MUPs has been largely eliminated in inbred laboratory mice (Robertson, Cox, Gaskell, Evershed and Beynon 1996), and no MUP-congenic strains currently exist.

The evolution of this highly polymorphic and species-specific signal suggests that the use of MHC-associated odours in inbreeding avoidance may not be as widespread as is often assumed, particularly as the main evidence for a direct link between MHC scents and disassortative mating came from mouse studies. This does not rule out the possibility that MHC plays a role in mate choice and this may vary between species, but at present evidence remains ambiguous. A possible exception is the evidence for MHC allele counting in fish (Reusch et al. 2001; Aeschlimann, Häberli, Reusch, Boehm and Milinski 2003). The MHC of fish differs from that of tetrapods as these genes are organised in at least two separate linkage groups rather than occurring in a single tight complex (Sato, Figueroa, Murray, Malaga-Trillo, Zaleska-Rutczynska, Sultmann, Toyosawa, Wedekind, Steck and Klein 2000). Nevertheless, to demonstrate that MHC is of greater importance than the rest of the genome in determining mate choice, these studies still need to control adequately for background genetic relatedness to eliminate the possibility of a correlation between MHC and the marker actually used for inbreeding assessment.

## 6 Conclusions

The negative consequences of inbreeding for survival and reproductive success are well documented, and emphasise the fitness benefits of genetic heterozygosity. While there may be particular advantages to genetic heterozygosity at some highly polymorphic loci, there is currently little evidence to support the idea that animals choose partners specifically to maintain diversity at such regions. Instead, heterozygosity at these polymorphic loci may be maintained by the mechanisms that sustain genome-wide heterozygosity. Nevertheless, such regions may be used to recognize close relatives and avoid inbreeding. The likely evolutionary benefits of MHC heterozygosity, coupled with the highly detectable odours associated with this region, have led to the intuitively obvious conclusion that females should choose mates that will increase offspring MHC heterozygosity. Because this seems such a plausible hypothesis, evidence that the MHC does indeed appear to influence mate choice has rapidly led to the widespread acceptance of MHC disassortative mating. However while it undoubtedly follows that such behaviour should benefit choosing females, the evidence remains decidedly mixed. Experiments using MHC congenic strains of mice have produced conflicting results, and in any case bias the likelihood of detecting an effect by removing all other sources of variation. Attempts to correct for this have generally run into the opposite difficulty of disentangling the tight link between MHC and background. As a result, it remains possible that the disassortative mating behaviours attributed to MHC are in fact a consequence of mate choice on the basis of alternative, largely untested, cues associated with avoiding the substantial costs of inbreeding. MUPs appear to be one such system in house mice,

but other signals of inbreeding avoidance may well be widespread. We propose that evidence for MHC effects on mate choice needs to be more critically assessed, and the scope of research into polymorphic signals extended beyond just the MHC.

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