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MHC, mate choice and heterozygote advantage in a wild social primate

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Abstract

Preferences for mates carrying dissimilar genes at the major histocompatibility complex (MHC) may help animals increase offspring pathogen resistance or avoid inbreeding. Such preferences have been reported across a range of vertebrates, but have rarely been investigated in social species other than humans. We investigated mate choice and MHC dynamics in wild baboons (*Papio ursinus*). MHC Class II *DRB* genes and 16 microsatellite loci were genotyped across six groups (199 individuals). Based on the survey of a key segment of the gene-rich MHC, we found no evidence of mate choice for MHC dissimilarity, diversity or rare MHC genotypes. First, MHC dissimilarity did not differ from random expectation either between parents of the same offspring or between immigrant males and females from the same troop. Second, female reproductive success was not influenced by MHC diversity or genotype frequency. Third, population genetic structure analysis revealed equally high genotypic differentiation among troops, and comparable excess heterozygosity within troops for juveniles, at both *Mhc-DRB* and neutral loci. Nevertheless, the age structure of *Mhc-DRB* heterozygosity suggested higher longevity for heterozygotes, which should favour preferences for MHC dissimilarity. We propose that high levels of within-group outbreeding, resulting from group-living and sex-biased dispersal, might weaken selection for MHC-disassortative mate choice.

Keywords: genetic diversity, mating systems, population genetics, reproductive strategies, sexual selection, social structure

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Introduction

Since the discovery of major histocompatibility complex (MHC) dependent mate choice in mice (Yamazaki *et al.* 1976), evidence for a role of the MHC in shaping mating preferences across a variety of taxa has been accumulating (recently reviewed by Milinski 2006; Piertney & Oliver 2006; Yamazaki & Beauchamp 2007). The MHC is a large cluster of highly polymorphic genes coding for the molecules involved in the adaptive (as opposed to innate) immune response. As a consequence, the evolution of MHC-dependent mate choice is expected to favour combinations of mates that will confer the strongest pathogen resistance to offspring. In view of both its codominant expression and its function in the immune response, individuals with a high MHC diversity may be at an advantage in a population facing heterogeneous pathogenic pressures (i.e. heterozygote advantage: Doherty & Zinkernagel 1975), so that females are often expected to avoid inbreeding, or maximize offspring MHC heterozygosity, by selecting MHC-dissimilar mates (Brown 1997; Jennions & Petrie 2000; Tregenza & Wedell 2000; Neff & Pitcher 2005).

However, alternative (but not necessarily exclusive) models have been proposed to explain the maintenance of MHC polymorphism through pathogen-mediated

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selection, and these models generate different predictions regarding the targets of MHC-dependent mating decisions. First, the effects of thymic selection on T-cell repertoires (Lawlor *et al.* 1990; Nowak *et al.* 1992) might confer a better pathogen resistance to individuals possessing an intermediate (rather than maximal) MHC diversity. This would select for an intermediate level of dissimilarity between mates (Reusch *et al.* 2001; Jacob *et al.* 2002; Milinski 2006). Second, MHC diversity might also be maintained through two extra, distinct models: frequency-dependent selection or fluctuating selection (Apanius *et al.* 1997; Hedrick & Kim 1999; Spurgin & Richardson 2010). Under frequency-dependent selection, a particular allele is beneficial when rare, but disadvantageous when common, because natural selection favours parasites that can evade the MHC-dependent immunity of the most common host genotypes, decreasing the fitness of individuals possessing common alleles. Under fluctuating selection, pathogenic pressures will vary across space and time, favouring particular alleles in one environment but others elsewhere or later. Under each of these models, the evolution of directional preferences for locally adaptive MHC genotypes should be favoured over non-directional choice for optimally or maximally dissimilar genotypes.

Early work on MHC-associated mating preferences mostly took place in controlled laboratory conditions and demonstrated the existence of MHC-disassortative mate choice in rodents (reviewed by Jordan & Bruford 1998). These studies further suggested that such preferences were mediated by odour phenotypes, although subsequent experimental studies in mice have highlighted the potential importance of other polymorphic genes (e.g. the major urinary proteins (MUP) complex) for kin discrimination and inbreeding avoidance based on odour phenotypes (Sherborne *et al.* 2007). Nevertheless, studies of MHC-dependent mate choice have since accumulated in natural populations, reporting a variety of results. Studies encompassing a range of organisms from fish (e.g. Landry *et al.* 2001; Consuegra & de Leaniz 2008) to mammals (Schwensow *et al.* 2008a,b), including reptiles (Olsson *et al.* 2003; Miller *et al.* 2009) and birds (Freeman-Gallant *et al.* 2003), have reported choice for MHC-dissimilar partners. In contrast, recent work has suggested that animals may prefer optimally rather than maximally dissimilar partners (birds: Bonneaud *et al.* 2006; fish: Reusch *et al.* 2001; Milinski *et al.* 2005; Forsberg *et al.* 2007). According to still further studies, partner preferences target mates possessing maximal MHC diversity (e.g. birds: Richardson *et al.* 2005; mammals: Sauermann *et al.* 2001) or specific MHC genotypes (mammals: Ditchkoff *et al.* 2001; birds: von Schantz *et al.* 1996; Ekblom *et al.* 2004). Finally, contrary to all these studies, no MHC-dependent mate choice of any sort could be detected in some other species and populations (mammals: Paterson & Pemberton 1997; birds: Westerdahl 2004), suggesting that it is not a ubiquitous vertebrate strategy.

In line with this, the importance of MHC for human mate choice has generated considerable debate. Studies focussing on relatively isolated human populations characterized by low levels of migration suggest that MHC dissimilarity plays a role in human mate choice (Ober *et al.* 1997; Chaix 2008), while studies in other populations found no influence of MHC dissimilarity (Hedrick & Black 1997; Ihara *et al.* 2000; Chaix *et al.* 2008). Although less direct, studies of MHC-correlated preferences through the now famous 'sweaty T-shirt' experimental protocols have similarly produced mixed evidence (Wedekind *et al.* 1995; Wedekind & Furi 1997; Jacob *et al.* 2002; reviewed by Havlicek 2009). Extending the focus to non-human primates does not clarify the picture. An initial study of a captive group of rhesus macaques found no evidence of mate choice for MHC dissimilarity, although MHC-heterozygous males enjoyed higher reproductive success (Sauermann *et al.* 2001). In contrast, recent work in a captive, inbred (Charpentier *et al.* 2006), colony of mandrills did report MHC-disassortative mate choice, as well as choice for MHC- and genome-wide diversity (Setchell *et al.* 2009). Studies in natural populations of non-human primates, which have thus far been limited to two sympatric populations of Malagasy lemurs, i.e. pair-living fat-tailed dwarf lemurs (Schwensow *et al.* 2008b) and solitary foraging grey mouse lemurs (Schwensow *et al.* 2008a), similarly found female choice for both MHC dissimilarity and diversity, as well as for males with high genome-wide heterozygosity.

Overall, the inconsistencies reported across species and populations suggest that patterns of MHC-dependent mate choice may be context-dependent (Roberts 2009). Specifically, behavioural and demographic factors, by altering the genetic structure of populations, may in turn influence the occurrence and benefits of MHC-dependent mate choice. Consequently, documenting patterns of mate choice together with its potential indirect benefits (e.g. MHC-dependent survival or parasite resistance) in any given population appears crucial to gain a more general understanding of the relevance of MHC for mate choice in natural populations.

This paper integrates tools from behavioural ecology and population genetics to investigate the links between reproductive strategies and MHC dynamics in a natural population of group-living primates: chacma baboons (*Papio ursinus*). Baboons live in large multimale–multifemale groups characterized by female philopatry and male dispersal. Male baboons may express mating preferences in two ways: through their choice of group membership when transferring between groups (preferring groups with the best possible range of female

mates), and their choice of individual female once in a group. In the first case, males typically move from one group to another several times over their lifetime. However, dispersal is associated with several costs, split between those incurred during the solitary period such as higher predation risk and lost mating opportunities (Alberts & Altmann 1995), and those associated with recent entry into a new group such as social isolation, low social rank, and increased rates of aggression (Strum 1987). Overall, these costs are likely to limit the number of dispersal events in a male's lifetime, and encourage males to select their group carefully. In the second case, once in a group, males may choose particular females when establishing consortships. Although baboon males typically try to monopolize as many females as possible, they have been found to express preferences (for instance, when several females are sexually receptive simultaneously) for females who are multiparous over nulliparous (i.e. those that have given birth to several infants over those that have never given birth) (Gesquiere *et al.* 2007), who are closer to ovulation (Gesquiere *et al.* 2007), and who display larger sexual swellings (Domb & Pagel 2001; Huchard *et al.* 2009). Female choice, in contrast, is largely constrained by the alpha male monopoly in multimale cercopithecine groups, although female strategies might still exert some influence on patterns of mating and paternity (Bercovitch 1995; Setchell *et al.* 2009).

In the first step, we combine a detailed analysis of patterns of dispersal and parentage with a broader approach based on population genetics to investigate the existence of MHC-dependent mate choice in baboons. Specifically, we test four hypotheses: an animal may seek a partner possessing maximally dissimilar genes from his/her own (hypothesis H1), a partner possessing optimally dissimilar genes from his/her own (hypothesis H2), a partner with high MHC diversity (H3), and/or a partner with rare MHC genes (H4). These hypotheses, which are not mutually exclusive, generate testable predictions at both individual and population levels (Table 1).

In the second step, we explore a potential benefit of MHC-disassortative mate choice by testing the hypothesis that MHC-heterozygous individuals are at an advantage: by comparing the distribution of neutral (microsatellites) and adaptive (MHC) genetic heterozygosity with respect to age, we test the prediction that MHC heterozygotes should be more frequent in older individuals if they survive longer.

Throughout, we focus on one highly variable and immunologically important region of MHC genes known as *Mhc-DRB*. While these genes represent less than 20% of the total MHC complex in humans (Horton *et al.* 2004), they play an important role in parasite resistance (e.g. Paterson *et al.* 1998; Wegner *et al.* 2003; Schwensow *et al.* 2007; Oliver *et al.* 2009) and have a significant influence on mate choice in a variety of populations and species, including primates (Schwensow *et al.* 2008a,b; Setchell *et al.* 2009).

Materials and methods

Study population and data collection

Data were collected from six groups and two solitary males captured in a wild population of chacma baboons living at Tsaobis Leopard Park, on the edge of the Namib Desert in Namibia, Southern Africa (see Table S1, Supporting information). Age was estimated through dental examination (Huchard *et al.* 2009). Tissue samples for DNA analysis were obtained from 199 individuals and stored in a DMSO–salt solution; additional non-tissue DNA samples were obtained from 11 individuals (see Supporting information for further details).

Microsatellite and Mhc-DRB typing

A total of 210 individuals were genotyped across 16 microsatellite loci (see Supporting information), and 199 of these individuals were also genotyped at the highly polymorphic *Mhc-DRB* exon 2 (MHC Class II), including the entire antigen-binding region. As in humans, the

Table 1 Summary table of the hypotheses tested

Mate choice based on	Predictions
(H1) Maximally dissimilar genes	Genetic dissimilarity between immigrant males and females
	Genetic dissimilarity between two parents of the same offspring
	MHC heterozygote excess within troop high relative to neutral expectation in juveniles
(H2) Optimally dissimilar genes	Negative correlation between the alleles of two parents of the same offspring
(H3) High MHC diversity	Male choice for females with high MHC diversity
	High reproductive success of females with high MHC diversity
(H4) Rare MHC genotypes	Male choice for females with rare MHC genotypes
	High reproductive success of females with rare MHC genotypes
	MHC heterozygote excess within troop high relative to neutral expectation in juveniles

number of *Mhc-DRB* genes in baboons can vary from individual to individual: in our study population we found a maximum of four *DRB* loci. The molecular methods used for *Mhc-DRB* genotyping in this population have been described previously (Huchard *et al.* 2006; Huchard *et al.* 2008), and involve the use of PCR, denaturing gradient gel electrophoresis and direct sequencing. Only those individuals genotyped at both neutral markers and *Mhc-DRB* were included in the analyses presented here, with the exception of the parentage analysis (which included all animals). Twenty-three distinct *Mhc-DRB* sequences (GenBank Accession nos DQ339722–DQ339737 and EU244816–EU244822) were identified. These were non-randomly associated within individuals, defining haplotypes. Haplotypes were deduced from segregation analysis within mother–infant pairs and subsequently confirmed by patterns of linkage disequilibrium (Huchard *et al.* 2008). Fifteen haplotype configurations were identified, each carried by 1 (0.025%) to 52 (26%) individuals and comprising 1–4 *Mhc-DRB* sequences. MHC molecules exhibit some degree of overlap in their antigen-binding affinities (e.g. Southwood *et al.* 1998). MHC molecules binding similar antigens can thus be grouped in a supertype, the biological relevance of which is now supported by a growing body of evidence (e.g. Sette & Sidney 1998; Trachtenberg *et al.* 2003; Schwensow *et al.* 2007). We classified baboon *Mhc-DRB* sequences as 12 discrete supertypes, on the basis of the physicochemical amino acid properties of the nucleotides found to be under positive selection (i.e. exhibiting higher rates of non-synonymous relative to synonymous mutations) and thus assumed to be involved in antigen binding and processing by the MHC molecule. Full details regarding haplotype definition and supertype classification are provided in Huchard *et al.* (2008).

In this paper, we measured individual *Mhc-DRB* diversity using two estimators: the number of distinct *Mhc-DRB* sequences and the number of distinct *Mhc-DRB* supertypes. Since the identification of alleles at specific *Mhc-DRB* loci is not possible using our methods, an individual carrying two different *Mhc-DRB* haplotypes is here considered as *Mhc-DRB* heterozygote. Haplotypes displayed 1–4 *Mhc-DRB* sequences, thus individuals exhibited 2–8 different *Mhc-DRB* sequences (mean ± SD: 5.38 ± 1.60) or supertypes (mean ± sd: 4.96 ± 1.47). To ascertain the role of rare MHC genes, we used *Mhc-DRB* genotype frequency (e.g. frequency of the considered genotype in the study population). In our data set, *Mhc-DRB* heterozygosity is correlated with: (i) the frequency of the rarest haplotype carried by each individual (Spearman correlations, $n = 199$, $\rho = -0.40$, $P < 10^{-3}$); and (ii) both estimators of individual *Mhc-DRB* diversity (Spearman two-tailed correlation tests, $n = 199$, number of *Mhc-DRB* sequences: $\rho = 0.55$, $P < 10^{-3}$; number of *Mhc-DRB* supertypes: $\rho = 0.52$, $P < 10^{-3}$).

Paternity assignment, measures of relatedness, and neutral heterozygosity

Using 16 microsatellites, we calculated an index measuring individual neutral heterozygosity as well as pairwise coefficients of relatedness between all males and females (see Supporting information). Pairwise relatedness was estimated by a triadic likelihood method implemented in the software package COANCESTRY (Wang 2007). Note, however, that the use of 16 microsatellite loci might not provide an accurate reflection of the overall genetic diversity within individuals (deWoody & deWoody 2005; but also Aparicio *et al.* 2007). Parentage analysis was performed with 16 microsatellite loci and *Mhc-DRB* using two software packages: CERVUS version 3.0.3 (Kalinowski *et al.* 2007) and COLONY (Wang 2004). The results are presented in the Supporting information.

Statistical analyses

We first tested whether males choose to immigrate into a group according to the MHC genotypes of resident females. A total of 19 adult males were found to be immigrant based on either their capture history (e.g. a male captured in different troops over time), their reproductive history (a male that fathered infants in one group but was captured in another), or their low average relatedness to the resident females (see Supporting information). Five males were found to perform multiple transfers, and thus appear repeatedly in this sample, resulting in 25 dispersal events in total. In each case we calculated the average MHC similarity between the male and all the females in his current group of residence. MHC similarity D_{AB} between a male A and a female B was estimated as $D_{AB} = 2F_{AB}/(F_A+F_B)$, where F_{AB} is the number of the *Mhc-DRB* sequences shared by A and B, and F_A and F_B are, respectively, the number of sequences of A and B (Wetton *et al.* 1987). The same estimate was used to compare MHC supertypes and haplotypes between potential mates. The mean *Mhc-DRB* similarity based on the number of shared sequences between males and reproductive females from other groups differed significantly between the least and most similar groups [least similar: range = (0.00–0.29), mean ± SD = 0.16 ± 0.07; most similar: range = (0.33–0.66), mean ± sd = 0.45 ± 0.09; $n = 19$ males in both cases; Mann–Whitney paired test, $W = 17$, $P < 10^{-3}$]. This remained true when comparing the least similar group and the second most similar group (after excluding, for each male, his most similar group in case

it represents his natal group and thus might not constitute a candidate group for immigration) for all three parameters (sequences, supertypes, haplotypes: $P < 10^{-3}$ in each case). A distribution of these parameters under the null hypothesis was generated by randomly allocating males to groups 10 000 times. In each case, the *P*-value was computed as the proportion of cases displaying a lower or equal mean D_{AB} or pairwise relatedness value than the observed one.

We then investigated male mate choice in relation to female MHC genotype within groups. Using the distribution of estimated ages at offspring conception for each female, we calculated that 95% of conceptions occurred after the age of 5 years in our population (mean age of female at conception ± SD: 10.8 ± 3.31). Five years is also near to the reported age at first conception in other wild baboons (Bentley Condit & Smith 1997; Altmann & Alberts 2003; Cheney *et al.* 2004; Beehner *et al.* 2006). All females who were older than five at the time of the conception of a given infant and resident of the relevant group were therefore considered as potential partners for a male genitor. A distribution for both MHC similarity (measured as defined above) and relatedness for random partners was generated by randomly matching 10 000 times each genitor to one female from the pool of his potential mates. In this simulated sample, the variance in female reproductive success (measured by the individual number of surviving infants) did not differ from the observed value. The *P*-value was computed as previously described.

Note that a caveat applies to these randomization tests where animals, especially males, were allowed multiple appearances in the data set. This is inevitable in a social system where a few (i.e. dominant) males sire most of the offspring, resulting in 13 fathers involved in 59 conceptions. Although two different pairs cannot be considered as statistically independent if they involve the same male or female, using permutation tests limits the risk of false statistical inference in such a design. For instance, an individual possessing a rare genotype may increase the risk of false-positives if it makes multiple appearances, but our permutation test controls for this bias because such an individual will appear as many times in the random as in the observed distribution.

The influence of individual MHC genotype and neutral heterozygosity on female reproductive success was investigated for 64 sexually mature females from six different troops through the number of surviving infants. Maternities were inferred for 95 juveniles aged from 0 to 5 years by parentage analyses. Because females included in these analyses had not completed their reproductive life, reproductive success was indexed as the total number of viable offspring produced divided by the log-transformed number of reproductive years (calculated as age minus average age at first conception) of the individual concerned. Because troop identity was expected to generate non-independent estimates of reproductive success, and because our proxy for reproductive success was quasi-poisson distributed, we used a generalized linear mixed-model approach (lmer function in *R*) with group identity fitted as a random effect. Individual neutral heterozygosity was fitted as a fixed effect (to control for potential effects of genome-wide diversity), followed by either *Mhc-DRB* individual diversity (i.e. the number of distinct *Mhc-DRB* sequences, supertypes or haplotypes) or *Mhc-DRB* genotype frequency. We also fitted quadratic effects for the number of *Mhc-DRB* sequences and supertypes to test for a possible advantage of an optimal, intermediate level of MHC diversity. Comparable analyses on the reproductive success of males were not possible because captured males may have sired offspring in unsampled groups, rendering an estimation of their overall reproductive performance imprecise.

To test for a possible age structure in the distribution of *Mhc-DRB* heterozygosity, we used a binary mixed-effect model explaining the probability of being heterozygote for MHC by three fixed factors: age, sex and neutral heterozygosity; and one random factor: group membership. The significance of the variables was always tested using the full model (i.e. inferences were drawn with all predictors present) to avoid problems associated with stepwise model-selection procedures (Whittingham *et al.* 2006; Mundry & Nunn 2009). The significance of the fixed quantitative factors was systematically evaluated using χ^2 tests calculated according to the principle of marginality, testing each term after all others (i.e. comparing two models differing only in the presence of the tested fixed effect) (Pinheiro & Bates 2000). Twelve baboons were captured multiple times in different groups: 11 individuals were captured in two distinct groups and one was captured in three groups. For such individuals, age at the latest capture was used. All statistical analyses were carried out using software R 2.8.0 (R Development Core Team, 2003).

Population structure

Since each individual carried two *Mhc-DRB* haplotypes in our sample, *Mhc-DRB* was integrated into our population genetic analyses by treating *Mhc-DRB* as one locus and *Mhc-DRB* haplotypes as 'alleles' of known frequency. Genotypic associations between each pair of loci (16 microsatellite loci and *Mhc-DRB*) in each group were tested using the Raymond & Rousset probability test (Raymond & Rousset 1995a). Significant patterns were found in only 15 of 153 (10%) cases, none of which remained significant when accounting for multiple

testing. Deviations from Hardy–Weinberg equilibrium were tested using the exact *U*-score test of Rousset & Raymond (1995), where the alternative hypothesis is heterozygote excess. This test was initially carried out including the whole sample ($n = 199$ individuals) at each locus individually, i.e. without taking into account the group structure of the population. The tests revealed that one microsatellite locus (d16s402) was out of Hardy–Weinberg equilibrium after correcting for multiple testing (F_{IS} estimate = −0.432, $P < 10^{-4}$), and so potentially non-neutral (SI, Table S2). This locus was thus excluded from further tests and calculations involving the partitioning of genetic variation within and among groups.

Following these preliminary analyses, juvenile and adult cohorts were analysed separately throughout, fixing the value of 5 years as the cut-off between age classes. This figure prevents grouping young females with their first offspring together in the same cohort (see above). Deviations from Hardy–Weinberg equilibrium were then tested (using the above procedure) across groups at each locus. Global tests across groups were also performed across all neutral loci, according to the multi-sample extension of the score test (Rousset & Raymond 1995). Departure from Hardy–Weinberg equilibrium was measured with the F_{IS} estimator proposed by Weir & Cockerham (1984). Genotypic differentiation among groups was tested at each locus and across all neutral loci by calculating an unbiased estimate of the *P*-value of a log-likelihood (*G*) based exact test (Goudet *et al.* 1996). Population differentiation was measured using the F_{ST} estimator (Weir & Cockerham 1984). Calculations were performed using GENEPOP version 3.4 (Raymond & Rousset 1995b). The 95% confidence intervals for the F_{IS}-value calculated across groups and neutral loci ($n = 15$) was estimated using FSTAT v.2.9.3.2 (Goudet 1995).

Those individuals captured repeatedly over time were allowed multiple appearances in the data, so that our data set represents an exact snapshot of the demographic composition of each group at the time of capture. Nevertheless, to ensure that the resulting pseudoreplication did not alter our results, additional analyses were also performed with each individual included solely in the group where it was first captured. The results (Table S5, Supporting information) do not differ from those obtained in the full analysis.

Results

Do male baboons exhibit MHC-dependent mate choice (H1-4)?

A preference for MHC-dissimilar mates was investigated in relation to both male dispersal and mating decisions. In the first case, the observed value of mean *Mhc-DRB* dissimilarity between dispersing males ($n = 19$ males, 25 transfers) and the reproductive females in their new group ($n = 68$ among six groups) did not differ significantly from those simulated by randomly allocating males to groups within the population for any of the three measures of dissimilarity investigated (Table 2). In the second case, patterns of male mate choice were analysed for the parents of 59 conceptions identified from parentage inference, involving 13 males and 47 females, among a pool of 58 potential female partners. This analysis included 16 full-sibs (the mean maternal half-sibship size was 1.60 and the mean paternal half-sibship size was 4.21). Once again, the observed value of genetic dissimilarity between parents did not significantly deviate from the simulated values based on random mate selection within the pool of available partners for males, for any of the three measures of dissimilarity assessed (Table 2). These findings suggest that males do not base either their group immigration decisions, or their mating decisions within groups, on female MHC dissimilarity (H1). Similarly, there was no correlation between the individual MHC diversity of the mother and father of a given infant (Pearson's product–moment two-tailed correlation test, d.f. = 57, individual number of supertypes: $r_P = 0.05$, $P = 0.69$, individual number of sequences: $r_P = 0.16$, $P = 0.22$), suggesting an absence of mate choice aimed at producing offspring with an optimal, intermediate MHC diversity (H2). Finally, choice for genetically diverse partners (H3), or partners with rare MHC genotypes (H4), was also not detected (Table 2).

Does MHC genotype influence female reproductive success (H3, H4)?

We examined reproductive success, measured through the number of surviving offspring, in 64 sexually mature females with a number of infants ranging from 0 to 6 (mean ± SEM: 1.60 ± 0.02). We could not detect any effect of *Mhc-DRB* heterozygosity, diversity, genotype frequency, or neutral heterozygosity on female reproductive success when controlling for female age and group membership (Table 3). This finding fails to support the hypotheses that individuals with high MHC diversity (H3), or rare MHC genotypes (H4) have higher reproductive success.

Does population structure exhibit excess MHC heterozygosity (H1, H4)?

Analysis of fixation indices F_{ST} and F_{IS} at neutral loci revealed high levels of population structuring and heterozygote excess in both adult and juvenile cohorts

Table 2 Results of the male choice analyses using permutation tests

Test	Parameter		Simulated mean [one-sided 95% confidence interval]	Observed mean	*P*-value	Minimum deviation (%) from random mating required for significance*
Choice for groups with dissimilar females (n = 19 males; 25 transfers)	*Mhc-DRB* similarity between immigrant males and females	Sequences	0.29 [0.26]	0.29	0.51	10
		Supertypes	0.48 [0.46]	0.47	0.29	4
		Haplotypes	0.22 [0.20]	0.22	0.32	9
	Relatedness between immigrant males and females		0.05 [0.04]	0.05	0.51	20
Choice for dissimilar mates (n = 59 conceptions)	*Mhc-DRB* similarity between mates	Sequences	0.36 [0.30]	0.36	0.5	17
		Supertypes	0.53 [0.49]	0.55	0.76	7
		Haplotypes	0.31 [0.26]	0.3	0.37	16
	Relatedness between mates		0.07 [0.05]	0.06	0.17	29
Choice for genetically diverse mates (n = 59 conceptions)	*Mhc-DRB* individual diversity	Sequences	5.53 [5.91]	5.63	0.7	6
		Supertypes	5.14 [5.47]	5.22	0.69	6
		Haplotypes	1.93 [1.97]	1.91	0.16	2
	Neutral heterozygosity (homozygosity per loci)		0.33 [0.36]	0.32	0.41	8
Choice for mates with rare MHC genotypes (n = 59 conceptions)	MHC genotype frequency		0.03 [0.025]	0.03	0.26	17

*Threshold deviation between true and random pairs required for reaching statistical significance for each parameter examined given the power of our analyses. Calculations are based on our sample characteristics and £ = 0.05, and percentage differences are obtained by dividing the 95% CI threshold by the mean of the simulated distribution. As an example, any deviation exceeding 10% of the value obtained under random mating regarding the average *Mhc-DRB* dissimilarity (based on sequences) of a male to the females resident in his troop would be detected.

Table 3 Results of the GLMMs analysing female reproductive success. Table includes the model fitted to calculate the parameters and tests of each variable considered, together with Akaike's Information Criterion, the model coefficients (Est), standard errors (SE), X^2-values, statistical significance (P)

Parameter		Model fitted	AIC model	Est+SE	X^2_1	P
Neutral heterozygosity (HL)		HL	52.7	−0.67 + 0.75	0.34	0.56
Mhc-DRB diversity	N. supertypes (Nsup)	HL+Nsup	54.39	0.05 + 0.06	0.32	0.57
	N. supertypes^2 (Nsup^2)	HL+Nsup+Nsup^2	55.65	−0.04 + 0.03	1.05	0.59
	N. sequences (Nseq)	HL+Nseq	53.89	0.08 + 0.06	0.81	0.37
	N. sequences^2 (Nseq^2)	HL+Nseq+Nseq^2	55.82	−0.01 + 0.03	0.88	0.64
Mhc-DRB heterozygosity	N. haplotypes (Nhap)	HL+Nhap	52.84	0.76 + 0.38	1.87	0.17
Frequency of *Mhc-DRB* genotype (MHCfreq)		HL+MHCfreq	54.62	−2.57 + 5.82	0.08	0.77

(Fig. 1). Thirteen (87%) microsatellite loci displayed a heterozygote excess (negative F_{IS}-values) in the adult cohort and 14 (93%) in the juvenile cohort. Global tests across groups and neutral loci revealed a significant excess of heterozygotes in the population in both cohorts (adults: $F_{IS} = -0.07$ with CI 99% = [−0.03;−0.10], $P < 10^{-3}$; juveniles: $F_{IS} = -0.11$ with CI 99% = [−0.06;−0.16], $P < 10^{-3}$). Differentiation among groups across neutral loci was also substantial and significant in both cohorts (adults: $F_{ST} = 0.04$, $P < 10^{-3}$, juveniles: $F_{ST} = 0.06$, $P < 10^{-3}$). For *Mhc-DRB*, the heterozygote excess in the adult cohort across groups was substantial ($F_{IS} = -0.11$, $P < 0.01$) and higher than the F_{IS}-value estimated across the neutral loci (exceeding its 99% CI). In contrast, the heterozygote excess at *Mhc-DRB* of juveniles approximated the lower bound of the 99% CI of

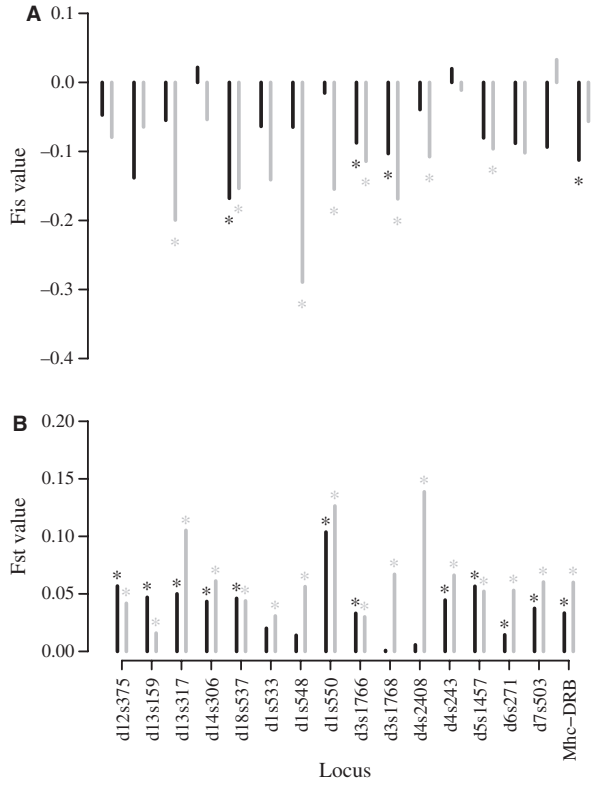

Fig. 1 Population genetic structure for 16 microsatellite loci plus *Mhc-DRB*. *F*-values for the adult cohort (n = 109 individuals) are displayed in black whereas values for the juvenile cohort (n = 99 individuals) are displayed in grey. Stars indicate values significantly different from those expected under random mating ($P < 0.05$). (A) Deviation from random mating, measured by F_{IS}-values. (B) Genotypic differentiation among groups, measured by F_{ST}-values.

the F_{IS}-value estimated across neutral loci ($F_{IS} = -0.06$, $P = 0.07$). Finally, differentiation among groups was also substantial at *Mhc-DRB* (adults: $F_{ST} = 0.03$, $P < 10^{-3}$, juveniles: $F_{ST} = 0.06$, $P < 10^{-3}$). The absence of heterozygosity excess at *Mhc-DRB* of juveniles relative to neutral markers does not match the predictions made for MHC-disassortative mate choice (H1) or choice for partners with rare MHC genotypes (H4).

Do MHC heterozygotes live longer than homozygotes?

Given the unexpected heterozygosity excess observed in adults (but not in juveniles) for *Mhc-DRB*, we tested whether the distribution of MHC heterozygotes varied across age classes. Age and sex were both significant predictors of *Mhc-DRB* heterozygosity (age: $X^2_1 = 4.94$, $P = 0.03$; sex: $X^2_1 = 3.95$, $P = 0.05$; Fig. 2). According to the model parameter estimates, and controlling for other variables in the model, one additional year increased the odds of being MHC heterozygote by 10%,

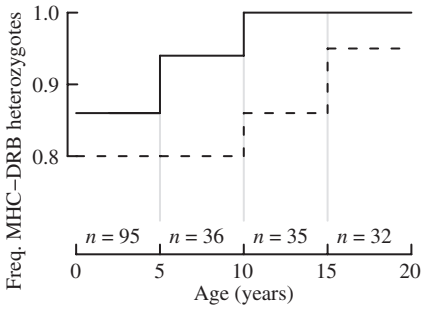

Fig. 2 Distribution by age of *Mhc-DRB* heterozygotes. The grey barplot shows the observed distribution of *Mhc-DRB* heterozygotes by age in the sample (n = 199 individuals) with the dashed line for females and the solid line for males.

while the odds that a male was MHC heterozygote was 2.48 times that of a female. The probability of being *Mhc-DRB* heterozygous was independent from wider genome heterozygosity, indexed by neutral heterozygosity ($X^2_1 = 1.81$, $P = 0.18$). Moreover, neutral heterozygosity was not correlated with age (Spearman correlation, $n = 199$, $\rho = 0.01$, $P = 0.91$). In contrast, age was positively correlated with both *Mhc-DRB* diversity (measured by the number of *Mhc-DRB* sequences: Spearman correlation, $n = 199$, $\rho = 0.15$, $P = 0.04$) and *Mhc-DRB* genotype frequency, but in this case only in the adult cohort (adults: $n = 102$, $\rho = -0.22$, $P = 0.02$; juveniles: $n = 97$, $\rho = -0.05$, $P = 0.64$).

Discussion

This paper investigates the influence of *Mhc-DRB* (class II) genes on the reproduction and longevity of wild chacma baboons by combining analyses of male dispersal, patterns of parentage and female reproductive success with a study of the population genetic structure. Despite using several complementary approaches at both the individual and population levels, we found no discernible preferences for partners with high *Mhc-DRB* dissimilarity or diversity, nor for partners possessing rare *Mhc-DRB* alleles.

Methodological considerations

The interpretation of negative results always requires caution. In our case, there are two points to consider. First, it should be emphasized that although some of our tests benefit from reasonable power, other analyses remain constrained by our modest sample size relative to the extensive MHC polymorphism present in our population (Table 2). Moreover, we could not test whether baboons choose mates possessing specific MHC genotypes, because we clearly lack the statistical power to detect significant changes in the frequencies of

specific *Mhc-DRB* genotypes from one generation to the next. Thus, it remains possible that baboons choose partners on the basis of specific MHC genotypes, as suggested by our recent finding that a specific MHC supertype influences the characteristics (size and shape) of female sexual swellings in this population (Huchard *et al.* 2010).

Second, because our analyses, like most studies of non-model organisms (Table 4), focus on a limited segment of the MHC, the interpretation of our results poses an important, but difficult question: are these results generalisable to the whole MHC region? If behavioural phenotypes are influenced by the whole MHC, and if genotyping an individual for a limited region (such as the *DRB*) poorly reflects its wider MHC genotype, then studies focusing on a limited fragment could produce biologically meaningless results. In theory, we could observe a pattern of apparent random mating with respect to any one locus in a situation where animals are mating disassortatively with respect to the whole region. Indeed, individuals that are found to be MHC-similar at any given MHC fragment might display dissimilarity with respect to other MHC fragments. Ideally, any study analysing MHC and mate choice should thus survey a large region of the MHC (i.e. class I and II genes), as has been done in some human studies (Ober *et al.* 1997; Ober 1999). This unfortunately requires a higher level of knowledge of the MHC structure than is presently available for most non-model organisms. The development of DNA-based MHC class I genotyping strategies is still in its infancy (Babik 2010) and few studies, to date, have identified MHC class I polymorphisms using non-model vertebrate DNA samples (see Table 4).

Despite such limitations, several lines of evidence suggest that studies focussing on MHC fragments can still play a valuable role in our understanding of the mechanisms and benefits underlying MHC-associated mate choice. First, a ground-breaking experimental study has shown that manipulating the female's perception of male genotype at MHC-Class IIB loci by adding peptides in the tank water of sticklebacks is sufficient to influence their mating decisions (Milinski *et al.* 2005). Second, trained congenic mice can choose between mates differing from a single-gene mutation of the H-2 complex (Yamaguchi *et al.* 1981). Similar experimental settings in (non-congenic) bank voles show that females prefer mates that are dissimilar at the *Mhc-DRB* (while the rest of the MHC region is unknown) independently of their relatedness (Radwan *et al.* 2008). Third, a number of studies on non-model organisms show that MHC-biased reproduction can prove detectable when looking at a limited MHC fragment (Table 4)—although publication biases inherently favour the report of positive results. Taken together, these results could simply arise from the strong linkage disequilibrium characterizing the MHC region (Stenzel *et al.* 2004; Kelley *et al.* 2005; de Bakker *et al.* 2006), meaning that genotyping an MHC fragment (such as *Mhc-DRB*) can be informative about the wider region, at least to some extent and in some species. But these results might alternatively reflect mating decisions genuinely targeting selective MHC regions. Indeed, the mating decisions of future parents, if mainly aimed at improving their offspring immunocompetence, should directly target those MHC loci that impact disease resistance most. In contrast, if mainly aimed at improving the overall genetic diversity of offspring in a context of inbreeding avoidance, mating decisions could then be expected to target the extended MHC region.

From an evolutionary perspective, deciphering whether animals target specific or extended MHC regions when choosing mates might thus help to document the nature of the genetic benefits of mate choice. This could be tackled by performing extensive genotyping of a population. As a first step, mating patterns could be related to the characteristics (e.g. diversity, dissimilarity) of each MHC region independently. As a second step, they could be linked to the characteristics of the MHC region taken as a whole. A detailed comparison of the results obtained through both approaches would prove invaluable. Nevertheless, before getting to this stage, studies of small MHC fragments still have the potential to make a valuable contribution to the field (as they have already done to date), but care should be taken not to extrapolate their results to the MHC region as a whole.

Mediators of selection for MHC-dependent mate choice

Beyond these considerations, our data suggest that male baboons do not choose their partners on the basis of *Mhc-DRB* diversity, dissimilarity or genotype frequency. Although female mate choice was not directly examined, the absence of an *Mhc-DRB* heterozygote excess (relatively to neutral variation) in the juvenile cohort indicates that females likewise do not choose partners on the basis of *Mhc-DRB* dissimilarity in our study population. One possible explanation for the absence of mate choice for MHC-dissimilar or MHC-diverse mates is that baboons are unable to discriminate a mate's MHC profile on the basis of odour. However, while anthropoid primates have long been thought to display poor olfactory abilities (Heymann 2006), recent research indicates that olfaction is more sensitive than is usually assumed in both non-human primates (e.g. Glaser *et al.* 1994; Laska & Seibt 2002; Heymann 2006) and humans (Shepherd 2004). Thus olfactory cues appear to play a role in

Table 4 Summary of studies on MHC-correlated mate choice in non-model organisms. It shows the species and type of population studied, the MHC loci screened, the design employed and sample size involved, as well as the main results (these relate only to MHC variation for simplicity and do not incorporate potential extra results regarding neutral genetic variation or pairwise relatedness). Note that an absence of choice simply indicates that choice has not been detected given the statistical power of the analysis cited. For comparison, human studies have recently been thoroughly reviewed by Havlicek and Roberts (2009)

Species	Population type	MHC region screened	Design and sample size	Results
Soay sheep (*Ovies aries*) (Paterson & Pemberton 1997)	Unmanaged domestic	5 microsatellites spanning Class I and II regions	Mating outcomes based on a minimum of 887 offspring	No choice for dissimilarity
Atlantic salmon (*Salmo salar*) (Landry *et al.* 2001)	Wild caught	1 Class II B locus	Mating outcomes of 41M and 35F	Choice for dissimilarity
Three-spined sticklebacks (*Gasteosteus aculeatus*) (Reusch *et al.* 2001)	Wild caught	1–6 Class II B genes	Two-way odour choice experiments respectively incl. 21F (choice for dissimilarity) and 29F (choice for diversity)	No choice for dissimilarity but choice for intermediate diversity
Rhesus macaques (*Macaca mulatta*) (Sauermann *et al.* 2001)	SFR; genetically isolated	Class II DQB1	Mating outcomes from 541 pairs (mate choice) and 120M (reproductive success)	No choice for dissimilarity; increased RS for heterozygote M
Savannah sparrows (*Passerculus sandwichensis*) (Freeman-Gallant *et al.* 2003)	Wild	Class II B haplotypes deduced by RFLP	Behavioural choice of 46 pair-living F (with known social partner) incl. 43 unfaithful F	Yearling F avoid similar M; probability of EP mating increases with similarity within pairs
Sand lizards (*Lacerta agilis*) (Olsson *et al.* 2003)	Wild or wild-caught	Class I haplotypes deduced by RFLP	Experiments: two-way odour choice experiments with 20F; field: observed pairing of 45 males and 46F	Experiments: choice for dissimilarity; field: male body mass correlates with female dissimilarity
Great snipe (*Gallinago media*) (Ekblom *et al.* 2004)	Wild	1–2 Class IIB loci	32 behavioural choice events of F in leks; mating success of 83M	No choice for dissimilarity, diversity or rare alleles; mated-males display specific MHC-lineages compared to non-mated males
Great reed warblers (*Acrocephalus arundinaceus*) (Westerdahl 2004)	Wild	1–6 MHC Class I loci	279 female choice events in leks	No choice for dissimilarity or heterozygosity
Three-spined sticklebacks (*Gasteosteus aculeatus*) (Milinski *et al.* 2005)	Wild caught	Class II B loci	Two-way odour choice experiments with 51F	Choice for intermediate MHC diversity
Seychelles warblers (*Acrocephalus sechellensis*) (Richardson *et al.* 2005)	Wild	2–4 Class I loci	Behavioural choice incl. 53 social and 31 extra-pair choice events	No choice for dissimilarity or intermediate diversity; EP mating more likely when social mate has low diversity; diversity of EP mates > social mates
House sparrow (*Passer domesticus*) (Bonneaud *et al.* 2006)	Wild	1–6 Class I loci	Behavioural choice of 46F and 56 M incl. 30 pairs	Positive correlation between diversity of social partners; low mating success of M with low diversity and low dissimilarity to F
Brown trout (*Salmon trutta*) (Forsberg *et al.* 2007)	Wild caught	1 Class II B locus	Mating outcomes of 24F and 24M	F choice for intermediate dissimilarity

Table 4 (Continued)

Species	Population type	MHC region screened	Design and sample size	Results
Grey mouse lemur (*Microcebus murinus*) (Schwensow *et al.* 2008a)	Wild	1–2 Class II DRB loci	Behavioural choice of 21F; mating outcomes based on 79 offspring	No precopulatory choice for dissimilarity or diversity; mating outcomes reveal choice for dissimilarity and diversity
Fat-tailed dwarf lemurs (*Cheirogaleus medius*) (Schwensow *et al.* 2008b)	Wild	1–2 Class II DRB loci	21 social pairs with 43 offspring incl. 17 EP youngs	Choice for dissimilarity and diversity for both social mates and fathers; no higher diversity of EP young.
Chinook salmon (*Oncorhyunchus tshawytscha*) (Neff *et al.* 2008)	Captive	1 Class II B locus	Mating outcomes in 3 groups of 36 fish with manipulated sex-ratios (total: 54F and 54M)	F choice for dissimilarity, no M choice for dissimilarity
Atlantic salmon (*Salmo salar*) (Consuegra & de Leaniz 2008)	Wild caught or hatchery-reared	1 Class IIα locus	Comparisons between individuals mating freely or not, incl. 122M and 123F	F choice for dissimilarity
Bank vole (*Clethrionomys glareolus*) (Radwan *et al.* 2008)	Captive	1 Class II DRB locus	Two-way odour choice settings with 20F	Choice for dissimilarity
Mandrill (*Mandrillus sphinx*) (Setchell *et al.* 2009)	SFR; genetically isolated	1–4 Class II DRB loci	Mating outcomes based on 180 offspring; reproductive success of 40M	Choice for dissimilarity and diversity
Tuatara snake (*Sphenodon punctatus*) (Miller *et al.* 2009)	Wild	3 Class I loci	Behavioural choice with 72 pairs incl. 67F and 61M	Choice for dissimilarity
Three-spined sticklebacks (*Gasteosteus aculeatus*) (Kalbe *et al.* 2009)	Laboratory-bred	Class II B loci	Mating outcomes based on 2279 eggs	Highest lifetime RS for M and F with intermediate diversity
Red junglefowl (*Gallus gallus*) (Gillingham *et al.* 2009)	Captive	2 Class I and 4 Class II loci	Two-way mate choice settings with 27M	M allocated more sperm to MHC-dissimilar females
Tiger salamanders (*Ambystoma tigrinum*) (Bos *et al.* 2009)	Wild	1 Class IIβ locus	Two-way mate choice settings with 36F	F choice for similarity
Three-spined sticklebacks (*Gasteosteus aculeatus*) (Eizaguirre *et al.* 2009)	Wild caught	Class II B loci	Mating outcomes based on 4000 eggs	F choice for intermediate diversity and for specific genotypes
Great snipe (*Gallinago media*) (Ekblom *et al.* 2010)	Wild	1–2 Class II B loci	Cor.: mating success of 79M	Increased mating success for M with locally common alleles

EP, extra-pair; F, females, M males; RFLP, restriction fragment length polymorphism; RS, reproductive success; SFR, semi-free ranging.

chacma baboon mating behaviour (Clarke *et al.* 2009) and to convey information about sex, male status and individual identity in mandrills (Setchell *et al.* 2010). In addition, humans can discriminate dissimilar MHC genotypes among potential mates on the basis of odour (Wedekind *et al.* 1995; Wedekind & Furi 1997; Jacob *et al.* 2002). A second possibility is that social constraints might limit the potential for MHC-disassortative mate choice in group-living mammals, as suggested by a previous study on Soay sheep (e.g. Paterson & Pemberton 1997). In group-living primates, at least two social factors might constrain mate choice in relation to MHC: dominance hierarchies and group size. As previously noted, the monopolization of mating opportunities by alpha males limits mate choice for subordinate males, and this would be particularly true in small groups and non-seasonal breeders where choice may be limited even for the alpha male (Cowlishaw & Dunbar 1991; Alberts *et al.* 2006). However, mate choice for MHC dissimilarity and diversity has recently been reported in a captive colony of mandrills (Setchell *et al.* 2010) where, like in baboons, alpha males exert tight control on mating opportunities (Setchell *et al.* 2005). This suggests that poor olfactory abilities or within-group social constraints cannot fully explain the absence of MHC-dependent mate choice in our study population.

There is one further way in which sociality might influence selection for the production of MHC-diverse offspring: namely, that the structuring of the population into social groups influences genetic variation in such a way that selection for MHC-dissimilar mates is reduced. Fundamental to this argument is our finding that the genetic structure of our population followed two crucial trends predicted for species with breeding groups and sex-biased dispersal (Chesser 1991; Sugg *et al.* 1996). First, there was genotypic differentiation among groups (indexed by F_{ST}-values), which can be interpreted as a direct consequence of female philopatry (daughters recruited into the adult breeding pool at sexual maturity contribute to the buildup of genetic correlations) coupled with male reproductive bias (each juvenile cohort contains a number of paternal half-sibs given that only a few males sire most of the offspring in multimale baboon troops: e.g. Alberts *et al.* 2006). Second, and more importantly, there was an excess heterozygosity (indexed by F_{IS}-values) within groups with an average of 10% extra heterozygous offspring within groups compared to values expected under panmictic mating. Such an effect is predicted to arise from male immigration into unrelated groups, resulting in the crossing of gene pools from distinct maternal lineages even under random mate selection (Chesser 1991). This pattern has been described in several socially structured species, including wild primates (Pope 1992; Lawler *et al.* 2003) and a feral sheep population that similarly displays no MHC-disassortative mate choice (Paterson & Pemberton 1997; Coltman *et al.* 1999).

The possibility that selection for MHC-disassortative mate choice is weakened by the outbred nature of our socially structured population could also account for the inconsistency of our results with the recent report of mate choice for MHC dissimilarity in captive mandrills (Setchell *et al.* 2009) suffering from inbreeding depression (Charpentier *et al.* 2006). Interestingly, human studies have repeatedly found MHC-correlated mate choice in isolated and relatively inbred populations such as the Hutterites (Ober *et al.* 1997) or the Mormons (Chaix *et al.* 2008), whereas similar preferences were undetectable in more outbred populations (Hedrick & Black 1997; Ihara *et al.* 2000; Chaix *et al.* 2008). Our findings may therefore reflect a more general pattern in species where social structure and sex-biased dispersal locally result in high levels of outbreeding.

The age and sex distribution of Mhc-DRB heterozygosity: a heterozygote advantage?

Finally, the heterozygote excess found within groups was greater for *Mhc-DRB* than for microsatellites in adults, but not in juveniles. As the mutational model of MHC and microsatellite loci are different (infinite allele and stepwise, respectively), their respective level of allelic diversity might not be directly comparable. However, their extent of heterozygote excess can be compared across age classes. Our analyses highlighted that older individuals had higher *Mhc-DRB* heterozygosity than younger individuals, but no similar pattern could be detected for heterozygosity at neutral loci. The difference observed between microsatellites and *Mhc-DRB* regarding patterns of heterozygosity across age classes is more likely to reflect a survival advantage of *Mhc-DRB* heterozygous individuals than an effect of population dynamics. This suggests that *Mhc-DRB* heterozygotes live longer than homozygotes. Additional analyses in our population show that older individuals also have a greater *Mhc-DRB* diversity (measured by the number of *Mhc-DRB* sequences possessed) and carry rarer *Mhc-DRB* haplotypes. Given the importance of *Mhc-DRB* for pathogen resistance (e.g. Paterson *et al.* 1998; Wegner *et al.* 2003; Schwensow *et al.* 2007; Oliver *et al.* 2009), the improved survival of *Mhc-DRB* heterozygotes could be consistent with both of the main hypotheses proposed for the maintenance of MHC polymorphism by pathogenic pressures: the heterozygote advantage, where a high MHC diversity allows individuals to fight a wide array of pathogens (Doherty & Zinkernagel 1975), and the rare allele advantage, where rare MHC alleles confer better resistance than

frequent ones against current pathogens (Bodmer 1972). Indeed, these two hypotheses are not mutually exclusive since the inheritance of a rare haplotype will typically translate into heterozygosity (Apanius *et al.* 1997). Both might therefore have contributed to the generation of the age structure observed in *Mhc-DRB* heterozygosity here. However, and as emphasized earlier, there is strong evidence in primates, humans included, that the class II *DRB* loci show linkage disequilibrium with the class I region (Bontrop *et al.* 1999; Stenzel *et al.* 2004; Alper *et al.* 2006). Consequently, an estimator such as *Mhc-DRB* haplotype heterozygosity (unlike other measures such as the number of *Mhc-DRB* sequences) may reflect the inheritance of an entire set of MHC genes, rather than the *DRB* region only, and the observed pattern of biased longevity could also arise from wider MHC effects.

We also found that *Mhc-DRB* heterozygosity was greater in males than in females. This sex bias might be attributed to higher rates of mortality for homozygous males, since the sex difference in the distribution of *Mhc-DRB* heterozygotes is unbiased in the first 2 years of life: 17/20 (85%) heterozygotes in females against 20/23 (86%) in males. In fact, the proportion of heterozygotes seems to increase earlier in males (mostly before 10 years) than in females (mostly after 10 years) (Fig. 2). This might reflect the fact that subadult and young adult males face a higher risk of wounding (and subsequent infection) than females following conspecific aggression (Drews 1996), for instance, when they enter a new group after natal dispersal, or try to rise in rank during their prime (van Noordwijk & Van Schaik 2004). Sex differences in the risk of injuries might even start during childhood, for instance, if males engage in more rough-and-tumble play as in most polygynous species (Chau *et al.* 2008). In line with this, male chacma baboons have been reported to show lower survival rates than females from birth (Cheney *et al.* 2004). In contrast, selective pressures on females might intensify later in life, as they maintain high reproductive rates while growing older (e.g. Altmann & Alberts 2003a).

Evidence for an MHC heterozygote advantage has sometimes been found (Thursz *et al.* 1997; Carrington *et al.* 1999; Sauermann *et al.* 2001; Oliver *et al.* 2009), but demonstrating an influence of MHC heterozygosity on resistance to specific pathogens has often turned out to be an unexpectedly difficult empirical challenge (reviewed by Penn 2002). One problem has been that a heterozygote advantage may only be detectable under certain conditions, which may require either multiple (Penn *et al.* 2002; Oliver *et al.* 2009) or successive infections. In this context, using integrative measures of performance that indirectly reflect an individual's ability to fight a variety of pathogens over its lifetime, such as longevity or lifetime reproductive success, might facilitate the detection of selection for MHC heterozygosity (or diversity) (Apanius *et al.* 1997), as suggested by our results. Likewise, a reproductive advantage of MHC heterozygous males was found in a semi-free ranging colony of rhesus macaques, and interpreted to reflect an increased parasite resistance in heterozygous individuals (Sauermann *et al.* 2001). Additional support for past pathogen-mediated selection in the Tsaobis baboon population comes from molecular analyses of the *Mhc-DRB* sequences, which has identified nine codon sites under selection (i.e. exhibiting higher rates of non-synonymous relatively to synonymous mutations) within a sequence of 84 sites. Eight of these sites were identical to the antigen binding sites defined by homology with the human leukocyte antigen, suggesting that the corresponding amino acids played, or have played, an active role in the recognition, binding and processing of antigens by the baboon immune system (Huchard *et al.* 2008).

Conclusions

Taken together, our results indicate that baboons do not choose *Mhc-DRB* dissimilar or diverse partners, despite an apparent survival advantage experienced by *Mhc-DRB* heterozygotes. The genetic structure of the population may help resolve this paradoxical finding: social structure and strong sex-biased dispersal locally result in high levels of outbreeding, probably weakening any evolutionary pressure favouring MHC-disassortative mate choice. Overall, these results suggest that social structure may play a critical role in mediating the effects of MHC on mate choice.

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EH concentrates on understanding proximate and ultimate aspects of the evolution of primate social and mating systems. LAK's research focuses on the evolution of MHC genes in a range of primate and vertebrate species. Much of JW's work is concerned with developing population genetics models and methods of analysis of empirical data to address issues in evolutionary and conservation biology. MR has broad interests in evolutionary biology, currently revolving around the evolution of human societies, but has dedicated much of his earlier work to population genetics. Finally, GC's research focuses on behavioural ecology, population ecology, and conservation biology, using primates as a model system.

Supporting Information

Additional supporting information may be found in the online version of this article.

Table S1 Demographic composition of the six baboon groups involved in this study. The number (N) of individuals is given at the time of group capture. Estimates of total group size come from field observations. As no estimate is available for the total number of females in H Group, the figure provided here is based on the percentage of females observed in the other groups

Table S2 Characteristics of the 17 loci used for parentage analyses, together with the test results for deviation from Hardy-Weinberg equilibrium (using exact U-score tests). Ho: observed heterozygosity, He: expected heterozygosity, NS: Non-significant, *** $P < 0.001$

Table S3 Summary table of the parentage analysis for 133 offspring

Table S4 Summary table for the identification of immigrant males. A putative transfer group was identified based on the individual capture history or reproductive history (the group where an adult male was trapped or had sired offspring, respectively). For any given male, transfer into the group was deduced on the basis of three criteria as detailed in text. Letters in italic indicate group names

Table S5 Analysis of the population structure for neutral and *Mhc-DRB* loci. This analysis allows only one appearance per individual. N: number of individuals. Bold characters indicate significant values, with a significance threshold $\alpha = 0.05$

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