Sexual selection explains more functional variation in the mammalian major histocompatibility complex than parasitism

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Understanding drivers of genetic diversity at the major histocompatibility complex (MHC) is vitally important for predicting how vertebrate immune defences might respond to future selection pressures and for preserving immunogenetic diversity in declining populations. Parasite-mediated selection is believed to be a major selective force, generating MHC polymorphism, and while MHC-based mating preferences also exist in multiple species including humans, the general importance of mate choice is debated. To investigate the contributions of parasitism and sexual selection in explaining among-species variation in MHC diversity, we applied comparative methods and meta-analysis across 112 mammal species, including carnivores, bats, primates, rodents, and ungulates. We tested whether MHC diversity increases with parasitoid richness and relative host size (as an indicator of the potential mate choice), while controlling for phylogenetic autocorrelation, neutral mutation rate and confounding ecological variables. We found that MHC nucleotide diversity increases with parasitoid richness for bats and ungulates but decreases with parasitoid richness for carnivores. By contrast, nucleotide diversity increases with relative host size for all taxa. This study provides support for both parasite-mediated and sexual selection in shaping functional MHC polymorphism across mammals, and importantly, suggests that sexual selection could have a more general role than previously thought.

1. Introduction

A significant fraction of the mammal genome is dedicated to immune defence, and immune genes are well known for their genetic variability [1, 2]. Parasites have long been viewed as a major selective force in shaping host genetic diversity [3, 4], and the rate of adaptive evolution for genes that interact most directly with pathogens can be exceptionally high [5]. Sexual selection can also influence immunogenetic variation; in particular, the ‘good genes’ hypothesis for resistance to parasites has been invoked to explain why some animals hold mating preferences in the absence of direct benefits of being choosy [6]. Thus, direct effects of parasites on host fitness, combined with sexual selection for mates that might confer beneficial genes to progeny, are the two most likely forces shaping immunogenetic diversity in animals.

The major histocompatibility complex (MHC) is an ideal candidate for identifying factors that determine immune gene diversity, because it plays a crucial role in immune defence for virtually all vertebrates and can mediate mate choice in a variety of species, including humans [7, 8]. The MHC encodes glycoproteins that bind to foreign antigens and present them to T-cells, initiating an immune response [9]. There are two major groups of MHC genes: class I responds to intracellular pathogens and class II interacts with extracellular...
pathogens[10]. In particular, the class II DRBlocus has been extensively studied because of its high allelic diversity, and both diversity and specificity of the loci predict parasite resistance in animals[7]. The DRBexon2 region encodes the functionally important antigen-binding sites (ABS) that recognize pathogen peptides, with evidence of intense positive selection at codons along the sequence [10]. Because different ABS bind to different pathogen proteins, multiple alleles are required to confer resistance to diverse pathogen strains and species[9].

Past work showed that even endangered species (which otherwise harbor extremely low diversity based on selectively neutral loci) can display high MHC genotypic diversity[11–13] with such observations attributed to strong balancing selection operating on MHC loci[3,7]. Despite the potential for universally strong selection on MHC genes across vertebrate taxa, species do differ in their levels of MHC variability[14]. Some of this variation can be explained by differential parasite pressure across species [15], but mechanisms underlying among-species variation in MHC have rarely been studied in a comparative sense (but see[15–17]).

Theorists suggest that disassortative mating could also preserve allelic diversity across MHC loci [18], and numerous species, including rodents, fishes, birds, and humans and discern MHC genotypes based on factory and other cues[19–21], and prefer mates with complementary or dissimilar MHC genotypes[22,23]. A key challenge facing researchers studying mating choice and MHC-related ecological and demographic factors influencing the opportunity for and benefits of being choosy[24]. As a result, most studies showing MHC-based mating preferences within species are based on laboratory or captive experiments, and studies conducted on wild populations have shown mixed results[25,26].

Here, we use a comparative approach to investigate the relative influence of the two proposed main selective forces on MHC polymorphism: parasite-mediated selection and sexual selection. Our analysis focuses on mammals from five orders, as mammals have been relatively well studied for MHC variation, parasites and infectious diseases, and traits associated with sexual selection and reproductive skew. Key questions motivating this study were: (i) how does MHC diversity vary across mammal groups? (ii) are measures of allelic and nucleotide diversity elevated in species with higher potential for mate choice? (iii) is MHC diversity also elevated in species with greater parasite richness? and (iv) is there an association between parasite richness and degree of sexual selection, and how might this interaction shape the relationship with MHC polymorphism? We estimated the potential for sexual selection using relative testis size as an proxy for competition among male reproduction offsprings, as past work showed this measure is greater in species with promiscuous or polygamous (as opposed to monogamous) mating systems[27–29]. To further select pressures exerted by diverse parasite communities, we augmented existing data on parasites and pathogens (including viruses, bacteria, protozoa, helminths and arthropods) from free-living mammal populations [30–32]. We used phylogenetically informed analyses to test key predictors of immunogenetic diversity across species, controlling for the potential effects of host phylogeny, ecological traits and uneven sampling effort. We also used meta-analyses to compare effect sizes across taxa and to better support the generality of the findings. To our knowledge, this work represents the first test of the importance of sexual selection for explaining immunogenetic variation across a wider range of mammals.

2. Method and materials

(a) Major histocompatibility complex data

Sequence data for 112 mammal species were compiled from GenBank using Geneious version 5.6.3. We first performed a preliminary search within the key term ‘MHC class II DRB’, recovered all mammal sequences and retained sequences including exon 2 of the DRB locus. We also searched on Web of Science and Biosis using each previously identified species Latin binomial and MHC as key terms. Sequences from subspecies were combined at the species level, and we followed the taxonomy of Wilson & Reeder[33]. Primary taxonomy followed the nomenclature from the Global Mammal Parasite Database[30] and the dataset from Garamszegi & Nunn[15] to correspond with parasite data. For each species, we recorded the number of animals sampled at the DRB locus because more alleles tend to be discovered as more individuals are sequenced.

Sequences were grouped according to Order (Carnivora, Chiroptera, Primates, Rodentia and Artiodactyla), imported into Mega v. 5.34 and aligned by Muscle[35]. Because sequences differ in length, we trimmed all exon 2 sequences to 171bp to estimate substitution rates. We removed pseudogenes and alleles with nucleotide insertions or deletions that might represent non-functioning alleles. We also removed DRB alleles from primates, as this locus is thought to be non-functional[36]. We checked for duplicates within species and removed non-unique sequences. Final numbers of sequences were recorded as numbers of alleles per species. For analyses of allelic richness, we used residual from a regression analysis assuming log(number of alleles) on log(number of individuals sampled) to control for uneven sampling across species.

Rates of selection for functional variation is a biologically important measure of diversity, especially for sites that encode proteins responsible for binding to foreign peptides (ABS[10]). To estimate substitution rates, we used the most commonly used method[37] with correction for multiple substitutions at the same site[38]. MEGA v. 5.34 was used to compute within-species average for aminoacidic changing non-synonymous substitutions (dN) at 15 ABS based on[39]. We repeated this process for synonymous substitutions (dS) at ABS to provide a baseline for neutral substitution rates. We avoided using the ratio dN/dS at ABS as in[15], as correlations with ratios may be more difficult to interpret, being influenced by both the denominator and denominator. However, we sloan analysis using this ratio, and results were generally consistent (see the electronic supplementary material, figures S1 and S2, though power to detect significant associations was reduced owing to some species having no synonymous substitutions at the ABS). We considered using alternative ABS sites determined using the consensus of codon-based maximum-likelihood methods[40] applied to each main order sequence set (e.g. carnivore, bat, primate, rodent and ungulate). However, these predicted sites were strongly and significantly correlated with the 15 peptide-binding region residues determined based on protein crystallography (Pearson’s correlation ranged from \( r = 0.49, p < 0.01 \), primates, to \( r = 0.93, p < 0.001 \), rodents). In addition, these 15 sites are known to be involved with antigen binding and have been shown to be under positive selection across a diverse set of taxa (carnivores, rodents, and primates[41]; bats[42]). Therefore, we focus analyses on these documented 15 ABS sites, though analyses with putative taxon-specific ABS sites showed overall consistent results (see the electronic supplementary material, figure S3). The number of MHC alleles varies by allelic lineage [43] and by the number of duplicated DRBloci [44]. Because most species in our dataset are non-model organisms and because information is available on the specific
(b) Parasite data

Hosts exposed to more diverse parasite assemblages could experience selection for greater genetic diversity for resistance [16]. Because MHC class II genes recognize extracellular parasites, there might be stronger relationships between parasites with prominent extracellular stages (such as helminths, arthropods and some microbes) and measures of DRB diversity. We compiled parasite richness data for each host species using the Global Mammal Parasite Database (www.mammalparasites.org), the most comprehensive collection of published records of parasitic organisms from free-living mammals [30]. For each host species, we recorded parasite richness as the total number of viruses, bacteria, protozoa, helminths and parasitic arthropods, as defined at the species level based on current taxonomic schemes. We also recorded separately the numbers of helminths, thought to have strong coevolutionary relationships with their hosts, micro-parasites (viruses, bacteria and protozoa) and macroparasites (helminths and arthropods) to test whether some groups were more strongly associated with MHC class II diversity than others. We could not examine all parasitic subgroups (e.g., viruses and bacteria) individually owing to low numbers of some host taxa.

Parasite richness estimates depend strongly on research effort [45]; better-studied host species tend to have more parasites reported to infect them. We therefore controlled for uneven sampling effort among hosts using the total number of citations for each host species (using Latin binomials and common taxonomic variants) from Web of Science as an indicator of scientific effort per host. Following previous studies [15,31,46,47], we used citation count as a control for research effort instead of the cumulative number of individual host species sampled across all studies, since some studies did not publish the number of animals sampled and other studies had high sample sizes despite testing for only a single parasite. We used residuals from a regression analysis of log(parasite richness) against log(citation count) (\( R^2 = 0.45, F_{1,96} = 78.29, p < 0.001 \)) to estimate corrected parasite richness per host.

(c) Estimates of sexual selection and ecological traits

Genetic mating systems, and specifically the potential for female mate choice (as female endogamy is common in mammals) [48], is expected to influence the strength of sexual selection on the MHC. Female in monogamous or polygynous mating systems are likely to be more constrained in their choice for mates that can provide direct or indirect benefits [49]. By contrast, females in promiscuous or polygynandrous mating systems are expected to have greater opportunity to select among potential mates. Relative testes size (testes mass/body mass) was used as a proxy for female promiscuity and opportunities for mate choice, as this measurement has been shown to predict sexual selection and mating system across mammals (e.g., primates [27], rodents [28], carnivores [29]) and it is available for a large number of species. We compiled testes mass data and male body mass from the literature (see the electronic supplementary material, dataset S1). In some instances, only testes length, circumference or volume measurements were available, and in those cases, we converted these data to mass using the method of [27]. We then used the residuals from a regression analysis of log(testes mass) against log(male body mass) to obtain relative testes size per species and performed this separately for each taxonomic group.

For eutherian mammals, we also compiled data on two variables that could strongly influence parasite resistance, mating behaviour, and/or MHC diversity and evolution. First, effective population size (\(N_e\)) can impact genetic diversity by affecting the realized mutation rate, strength of selection and the amount of genetic drift experienced by a population [50]. \(N_e\) can also influence parasite richness measures as larger populations can theoretically retain more parasites than smaller populations [51,52]. In addition, species with greater population density might have higher parasite diversities with density-dependent transmission [53], and species with larger geographical range sizes could encounter a range of differently sized populations [30]. Thus, we used census population size as an approximate measure of parasite richness [51,52]. We also used the ratio of parasitic richness to host body mass (\(\frac{\text{Parasite richness}}{\text{Host body mass}}\)) as a measure of parasite load.

(d) Comparative analyses

We tested whether log(MHC allelic diversity) and rates of positive selection (\(dN\) at functional sites; those that are positively selected) were associated with parasite richness and estimates of sexual selection. Because closely related species are more likely to share genetic and life-history traits [60], we used phylogenetic least-squares (PGLS) regression to control for phylogenetic structure through multivariable covariances [51,56]. We assessed the importance of each predictor through a stepwise model selection procedure, in which the full models included the following: corrected parasite richness (relative testes size), log parasite body mass, log population size, and the interaction between corrected parasite richness and relative testes size, while also including d S at ABS as covariates to control for underlying substitution rate. We then simplified the resulting models using Akaike information criteria (corrected for small sample sizes) [51] and removed variables that did not improve model fit (\(\Delta AICc > 4\)) to avoid problems associated with missing values in AIC-based model comparison where sample size changes as terms are removed, we removed any species from our dataset that did not have complete coverage for all of the predictor variables of interest in the starting full model. Tests for associations between relative testes size (as a response variable) and corrected parasite richness (as a predictor variable), we ran full PGLS models controlling for the effects of taxonomic group, log population size and male body mass. The PGLS regression was conducted using the caper package in R [63] using Pagel’s \(\lambda\) adjustment models for the auto regression signal observed in each variable. The phylogeny was constructed using the mammalian supertree [64] and polytomies were randomly resolved (by adding branches of length equal to zero) using the multi2clade function in the ape R package [65]. Species in the dataset but missing from the supertree assumed the names of the closest relatives (i.e. Papio cynocephalus was changed to Papio papio, Platanista gangetica was changed to Zalophus californianus).

To test the robustness of our results, we estimated taxon-specific effects sizes in the form of correlation coefficients [66] and ran meta-analyses to compare effects across different species. For each species, we used parallel analyses to examine differences in sample size and test for the influence of different factors.
3. Results

Our final dataset comprised 12 mammal species (2 carnivores, 14 chiropterans, 37 primates, 16 rodents and 19 ungulates), 2,454 sequences and 2,665 host-parasite species combinations (list of species with full trait and genetic datasets are provided in the electronic supplementary material, dataset S1 and S2). We tested for relationships between parasitism (using total parasiticerichness, helminth richness, and micro- and macro-parasite richness) and sexual selection (using relative testes size as an indicator of mating system) on the rate of positive selection (dN at cBS and MHC allelic richness across mammals. Analyses controlled for mammalian phylogeny, the rate of neutral substitutions (dS at cBS), measures of sampling effort and two host traits known to be important for parasitism (endogenous diversity based on previous studies (body mass and population size; electronic supplementary material, tables S1-S3)). All predictor and response variables except relative allelic richness and parasite richness showed strong phylogenetic signal and were more similar among closer relatives (see the electronic supplementary material, table S2).

Multivariate models showed that the strength of selection on cBS increased with relative testes size across all five mammal orders, tested here (figure 1a and the electronic supplementary material, table S1). Effect sizes differed among orders with approximately 64% of the variability attributed to heterogeneity among the true effects [67] (Q = 8.43, p = 0.04, I² = 63.84%), possibly owing to biological differences among mammal groups or the methodology used in different studies. When corrected for sampling effort for bats and ungulates and decreased with parasitism for carnivores (figure 1b and the electronic supplementary material, table S1).

Tests using data from parasite subgroups, including micro-parasites, macroparasites and helminths, showed that selection on cBS decreased with helminth and macroparasite richness for carnivores, and also decreased with micro-parasite richness for primates (figure 2; electronic supplementary material, figure S2). Ratios of N : dS increased with macroparasite and micro-parasite richness for carnivores and ungulates (see the electronic supplementary material, figure S2). Neutral substitution rate (dS at cBS) was positively predictor of N at cBS (see the electronic supplementary material, figure S4) but only in models without relative testes size (and larger sample sizes). Taxonomic group was also a significant predictor of allelic substitution at cBS, with both N and dS being highest for bats and primates and lowest for carnivores and ungulates (figure 3c).

We tested allelic richness as a separate measure of selection on cBS. This measure differed among mammal taxonomic groups and increased with population size for ungulates (electronic supplementary material, tables S1 and S3e) but did not depend on measures of parasite richness or testes size.

### Table 1

<table>
<thead>
<tr>
<th>(a) Taxa, N</th>
<th>Standardized effect size (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>carnivore, 12</td>
<td>0.87 (0.22, 1.52)</td>
</tr>
<tr>
<td>primate, 25</td>
<td>0.36 (−0.05, 0.78)</td>
</tr>
<tr>
<td>rodent, 11</td>
<td>0.95 (0.25, 1.64)</td>
</tr>
<tr>
<td>ungulate, 8</td>
<td>1.72 (0.85, 2.60)</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>(b) Taxa, N</th>
<th>Standardized effect size (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>carnivore, 14</td>
<td>−0.62 (−1.21, −0.03)</td>
</tr>
<tr>
<td>bat, 11</td>
<td>0.96 (0.26, 1.65)</td>
</tr>
<tr>
<td>primate, 27</td>
<td>−0.07 (−0.47, 0.33)</td>
</tr>
<tr>
<td>rodent, 14</td>
<td>0.17 (−0.42, 0.76)</td>
</tr>
<tr>
<td>ungulate, 15</td>
<td>0.77 (0.20, 1.33)</td>
</tr>
</tbody>
</table>

Fisher’s t transformed correlation coefficient

#### Figure 1

Forest plots showing predictors of the rate of non-synonymous substitutions (dN) at cBS. PGLS models show the effect of (a) relative testes size and (b) parasite richness, run separately for each mammal group. The vertical dotted line is positioned at zero and error bars denote 95% CI. N refers to the number of species included; RE model, random effects model. Heterogeneity test for relative testes size: Q = 8.433, p = 0.038, I² = 63.84%; parasite richness: Q = 17.408, p = 0.002, I² = 79.06%.

Allelic richness was significantly lower for ungulates than any other mammal group (figure 3). Apostoescu et al. [67] revealed that ungulates also show significantly fewer duplicated DRB loci than other mammal orders, whereas primates had the most (F1,38 = 8.359, p = 0.006; figure 3a).

Finally, we tested for a relationship between relative testes size and corrected parasitism richness, to ask whether the strength of sexual selection might covary positively with parasite pressure. Across all orders, we found a weak negative association between relative testes size and total parasite richness (p = 0.09; electronic supplementary material, figure S5a) with homogeneous effect sizes across taxa (Q = 1.079, p = 0.18, I² = 0.00%), although other components of parasite richness showed no trend (p > 0.1; electronic supplementary material, figure S5).

4. Discussion

We found evidence that pressure from a diverse parasitofauna (represented by corrected parasite richness at the host species level) was associated with positive selection at the MHC DRB locus in bats and ungulates only. Species in these two groups that harboured greater parasite richness also showed higher rates of functionally significant evolutionary change within the MHC. By comparison, greater potential for sexual selection (represented by relative testes size as a indicator of mating system) predicted greater positive selection on functionally important MHC sites across all five orders of mammals examined here.

Very few studies have considered predictors of cross-species variation in MHC polymorphism, and these conducted to date focused on the relationship between parasitrichness and MHC...
Figure 2. Forest plots showing predictors of the rate of non-synonymous substitutions at ABS. The results of PGLS models showing the effect of (a) macroparasite richness, (b) macroparasite richness and (c) helminth richness, run separately for each host and parasite group. Nominal analysis of random-effects models was found to be significant for the parasite predictor variables (p > 0.1). The vertical dotted line is positioned at zero for Fisher’s z transformed correlation coefficient. N refers to number of species; RE model, random effects model. Heterogeneity test for macroparasite richness: Q = 5.186, p = 0.159, I² = 43.24%; macroparasite richness: Q = 6.506, p = 0.089, I² = 55.08%; helminth richness: Q = 4.329, p = 0.228, I² = 0.00%.

allelic richness [15-17]. In spite of the extensive intraspecific empirical evidence for MHC-parasite associations (reviewed in [7,69]), there is surprisingly weak support for parasites driving variation in MHC diversity among species. One study found that allelic richness increased with helminth richness across 10 rodent species [16], and another study found that the rate of positive selection at ABS (but not allelic richness) was positively related to nematode richness (but not total parasite richness) across 27 primates [15]. Our study differed from prior studies by using genetic data from multiple populations (species), by including broader taxonomic groups in parasite richness estimates, by not delineating allelic lines of functional lineages, and by not separately analysing nematode richness (for which insufficient data were available from all species).

The negative relationship between parasite richness and measures of the strength of selection on MHC in carnivores ran counter to our expectations. One reason for this pattern could be due to interactions between threat status and infectious disease risk, such that carnivores might be more vulnerable to population bottlenecks and genetic drift that concurrently reduce their genetic diversity and increases their susceptibility to parasitism. Many high-profile threatened carnivores have depleted MHC diversity (wild dogs [70]; Ethiopian wolves [71]; cheetahs [72]) and have simultaneously experienced declines from introduced infectious diseases such as rabies, canine distemper and sarcoptic mange [73,74], these carnivore species might be exceptionally well studied and better represented in our dataset. One way to examine this issue further might beition to estimates of effective population size in comparative analyses and to distinguish between native versus introduced parasites and pathogens. An alternative explanation might involve differences in different stages of the evolutionary arms race. If parasites lead the game, evolvement might support parasitism-as-a-driver of MHC polymorphism (leading to a positive relationship). However, if hosts lead the game, greater MHC diversity might reduce parasite pressure (leading to a negative relationship).

In contrast to the taxon-specific evidence of parasite-mediated selection, we found that relative testes size, as an indicator of sperm competition and the potential for sexual selection to operate at the species level [27], was positively associated with the rate of evolution at ABS across all mammal groups in our study. This finding provides evidence that species with high potential for mate choice tend to have higher MHC nucleotide diversity at functionally important sites. There are several non-exclusive explanations for this result. First, species with greater relative testes size and sperm competition might have faster reproductive rates, increasing the speed of selection for new variants. Indeed, Sommer et al. [75] found higher levels of MHC variation in carnivores at ABS.

Figure 3. Genetic diversity at the MHC by mammal group. (a) The number of DRB loci, (b) relative allelic richness and (c) the rate of non-synonymous (d and N) and synonymous substitutions (d and S) at the ABS for carnivores, bats, primates, rodents and ungulates. Error bars denote 95% CIs. N refers to the number of species with data.
fast-reproducing and promiscuous rodents. Relative to monogamous and slower reproducing, relative, and hypothesized that slow reproduction might constrain MHC polymorphism. A second hypothesis is that greater sperm competition indicates greater promiscuity and increased exposure to sexually transmitted diseases, which could enhance selection on immune defences [76,77]. As a third possibility, females with more potential mates might select genetically complementary or non-related mates and by doing so, serve to increase MHC variability. A fourth hypothesis is that testes size is correlated with androgen levels [78], which can suppress immune function or mediate male behaviour and increase exposure to and selection by parasites [79,80]. Our finding of a weak negative relationship between parasitism richness and relative testes size however, is not consistent within this hypothesis. Importantly, each of these mechanisms predicts that greater promiscuity will lead to greater genetic diversity, a result already observed for MHC and neutral genetic diversity across passerine birds [81]. Our analysis did not support an interactive effect between parasite richness and relative testes size, as might be expected if both high parasite pressure and the potential for mate choice were necessary to drive high MHC diversity.

Our study strongly supported taxonomic group as an important predictor for MHC allelic and sequence diversity. Specifically, ungulates had significantly lower allelic richness than any other order, possibly owing to fewer duplicated DRBloc(c) [Figure 2a]. Primates, in comparison, had significantly greater allelic richness and more duplicated DRBloc. Average nucleotide divergence ($\pi$) is positively associated with the number of duplicated DRBloc in rodents [44] and this could be an important mechanism providing baseline genetic variation. Life-history traits or ecological conditions that affect the likelihood of MHC gene duplication events might therefore help predict MHC polymorphism in natural populations.

Overall, our study extends previous comparative work on MHC evolution by showing that both parasite-mediated selection and sexual selection can operate as independent forces maintaining differences in MHC diversity across mammal species. Evidence that parasites served as agents of selection was only found for bats and ungulates, but support for sexual selection was universal across mammal groups tested here. Potential explanations for this pattern may include greater selection on immune genes driven by higher pressure from socially or sexually transmitted disease, and greater opportunities for mate choice leading to fast rates of substitution. Importantly, our analyses emphasize that comparative studies can contribute to knowledge on MHC ecology and evolution. We expect results of this study will encourage more work on the influence of sexual selection on MHC variability in wild populations, with greater relevance for conservation genetics and predicting species responses to future disease risk.

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References


