

Detangling the mechanisms and timing of MHC-dependent sexual selection using Soay sheep

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Immune defence is a key component of fitness, and individuals are expected to have evolved preferences for mates that ensure immunocompetent offspring. Potential preferences include those for mates with specific heritable immune gene profiles ("good genes") or for immunogenetically dissimilar mates to increase offspring immune gene diversity. The major histocompatibility complex (MHC) is by far the most investigated immune gene in mate choice studies, but we still know very little about its role in sexual selection for genetic benefits. In this issue of *Molecular Ecology*, Huang *et al.* capitalize on the extraordinary wealth of behavioural, life history and genetic/genomic data from the free-living Soay sheep population on the Island of Hirta to address this problem. While the authors find evidence of both pre- and postcopulatory MHC-based sexual selection, postcopulatory MHC-dissimilar mate choice is indistinguishable from genome-wide effects, suggesting it is a byproduct of inbreeding avoidance in Soay sheep. The study's comprehensive sampling ensures that inferences are generalizable to the entire population and provides a gold standard for studies investigating immune gene-based sexual selection.

KEYWORDS

inbreeding avoidance, major histocompatibility complex, mate choice, Soay sheep

1 | INTRODUCTION

The evolution of mate choice for genetic benefits requires a continuous supply of genetic variation in the population to preserve the incentive to be choosy. Hamilton and Zuk's influential hypothesis (1982) proposed that co-evolution with parasites can maintain such supply of genetic variation in immune resistance genes that influence preferred traits. The major histocompatibility complex (MHC), vital for its role in the adaptive immune response, is by far the most investigated immune gene in mate choice studies (Winternitz & Abbate, 2022), and for good reason. It is one of the most polymorphic gene regions in vertebrates, and this diversity is believed to be maintained by pathogen-mediated balancing selection and sexual

selection (Radwan *et al.*, 2020). MHC-based sexual selection, including mate choice and post-mating selection, has been intensively studied, but despite more than 40 years of investigation, our understanding is limited. We still know very little about *which* MHC-based mechanisms may be at play, their *timing* during the mating process (i.e., pre- or post-copulatory) or their *importance* relative to genome-wide-based mating preferences such as inbreeding avoidance. Indeed, most studies are limited to questions that can be asked from a particular study system, with nonmodel populations producing the most evolutionarily relevant results but suffering from small sample sizes, patchy population data and incomplete MHC genotyping.

The study by Huang *et al.* (2021) in this issue of *Molecular Ecology* illustrates the complexity of identifying MHC-based sexual selection

by using an exceptional study system: the St. Kilda Soay sheep on Hirta (Figure 1). The Soay sheep (*Ovis aries*) is a primitive breed that was brought to the Scottish St. Kilda archipelago around 4000 years ago and has survived on the island of Soay ever since. In 1932, 107 Soay sheep were transferred to the neighbouring Island of Hirta where the population lives unmanaged and fluctuates between 600 and 2200 individuals. A part of the population has been the subject of a long-term individual-based study since 1985 (Clutton-Brock & Pemberton, 2004). Due to limited dispersal, relatively low genetic diversity and severe inbreeding depression (Stoffel et al., 2021), combined with significant fitness costs of parasites (Coltman et al., 1999; Hayward et al., 2011), Soay sheep should be under strong selective pressure to engage in nonrandom MHC-based mating. The authors comprehensively test key mechanisms of MHC-dependent sexual selection by combining over 30 years of detailed behavioural, life history, pedigree and genotype data (Figure 2a).

One major benefit of the Soay sheep system is the detailed genotype data. The genotyping includes full haplotype structure for seven expressed MHC class II loci as well as 37,000 genome-wide single nucleotide polymorphisms (SNPs) (Figure 2b). This data set allows the study to test if specific MHC mechanisms are under sexual selection (e.g., haplotype, heterozygosity and similarity-based mechanisms), as well as if the supported mechanisms are independent from signals found genome-wide (Figure 2c). Such genome-wide signals include, for example, inbreeding avoidance or mate preference for genome-wide heterozygosity. While many investigations of MHC-based sexual selection in natural populations have attempted to control for genomic effects by using microsatellite loci, studies have shown that genome-wide SNPs provide greater precision in estimating relatedness and individual-level heterozygosity, especially

for small populations (Lemopoulos et al., 2019). Increasingly affordable and feasible genomic approaches should offer more accurate inferences about the role of the MHC in nonrandom mating in future studies.

Another major advantage of the study is the thorough behavioural observations recorded during the mating season. Combining consort observations with parentage data allows the authors to differentiate MHC-dependent sexual selection at the pre- and postcopulatory stages (Figure 2d), which is rarely tested in natural populations. The authors find evidence that a particular male haplotype and female heterozygosity are disfavoured during the rut. These results suggest that male-male competition and male preference could play a role in precopulatory MHC-based sexual selection in Soay sheep. An alternative hypothesis for the overproportion of homozygous females was that these females may be less likely to conceive during their oestrus cycle, so appear more often in consort pairs. Whatever the mechanism, these results highlight that alternatives to female choice should be considered as mechanisms generating signals of sexual selection.

Finally, the present study implements an impressive sample size of 1710 adult sheep (889 female, 821 male) with complete genetic and behavioural data that are orders of magnitude larger than similar studies. Sufficient sample size is important for detecting relatively small effect sizes, common in sexual selection studies, that are estimated from natural, noisy and indirectly measured data sets (Jennions et al., 2012). Additionally, by sampling most of the population, the authors can say with high confidence that their findings are generalizable to the entire population.

Due to the notable amount of genetic, genomic and behavioural data amassed for an exceptional sample size, the study by Huang et al. (2021) currently represents a gold standard for MHC-based sexual selection studies. Given that genomic data are becoming increasingly available for nonmodel studies, one step for improvement would be making use of the genomics windows approach that is common in human MHC mate choice studies. This method compares the MHC with genomic regions of similar lengths and recombination rates to ask if the MHC is extreme in comparison to the rest of the genome in terms of similarity between mates (Chaix et al., 2008). Essentially, this approach specifically tests if patterns at the MHC between mates are independent of processes such as inbreeding avoidance or assortative mating that would affect the entire genome. Huang et al.'s study uses generalized linear mixed models with MHC haplotype sharing and genomic-similarity as separate variables in the same model. Because the MHC variable is not significant but the genomic variable is, they conclude that postcopulatory disassortative mating at the MHC is a byproduct of inbreeding avoidance, but they do not test for this explicitly. The genomic windows approach would allow for specific testing of this hypothesis but requires that the MHC and genome are well characterized, not a simple ask for most nonmodel species.

Another caveat of the current paper is that the Soay sheep system is relatively inbred, which makes it likely that MHC-based mate choice is advantageous and thus plays a role in this population.



FIGURE 1 A Soay sheep consort pair in the rut on Hirta, St. Kilda archipelago. Credit: Jill G. Pilkington

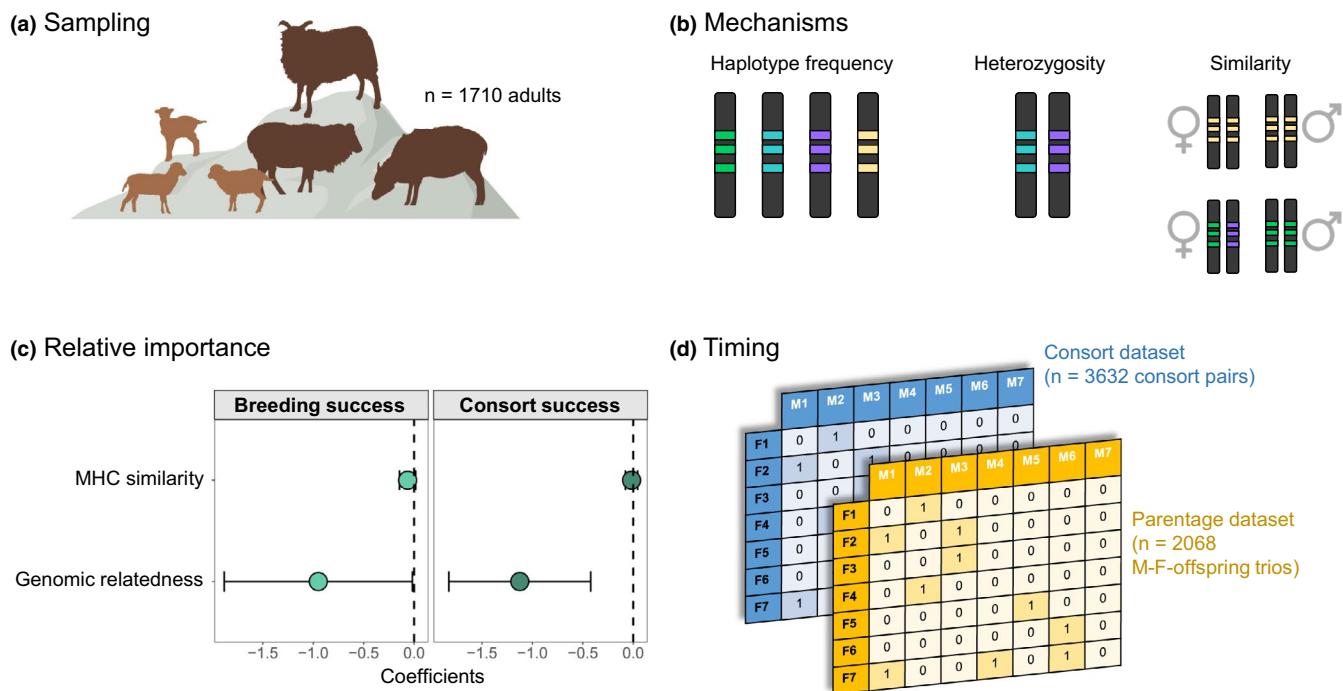


FIGURE 2 Illustration of methods used by the current study to identify different mechanisms of MHC-dependent sexual selection. (a) Sampling effort includes 1710 adult sheep, most of the Soay sheep population at the Village Bay area of Hirta. (b) Mechanisms of MHC-based mate choice tested include selection for MHC haplotypes, heterozygosity, and similarity between consorts and mates. (c) The relative importance of MHC-based mechanisms (e.g., MHC similarity) is inferred by comparing the strength of MHC-based effects to those generated for genome-wide-based metrics in the same model. Estimates with 95% confidence intervals that do not cross zero (dashed line) are significant. Data are from table 1 of Huang et al. (2021). (d) The timing (pre- or postcopulatory) of MHC-based mechanisms is determined by comparing the direction of MHC patterns between consort and parentage data. The data matrices represent all males and females within the data set for a given year. (0/1) indicate consort (blue) and breeding (gold) success for all combinations of female–male pairs

However, are the significant findings of MHC-based sexual selection in this study generalizable to other populations, or are Soay sheep an outlier due to their small, isolated and inbred status? Comparative studies that include population demographic history, genetic variation and inbreeding values would help resolve the outstanding question: Is MHC-based nonrandom mating a general phenomenon that depends on population diversity and extent of inbreeding? The current study raises expectations for data quality and comprehensive analysis that should inspire future study designs, helping to answer this question and advance understanding of immune gene-mediated sexual selection.

CONFLICT OF INTEREST

There is no conflict of interest to declare.

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DATA AVAILABILITY STATEMENT

No new data were generated for this perspective.

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