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ORIGINAL PAPER

Low MHC *DRB* class II diversity in the mountain goat: past bottlenecks and possible role of pathogens and parasites

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Abstract Major histocompatibility complex (MHC) genes are the most polymorphic in vertebrates and code for molecules playing a central role in pathogen resistance. We studied levels of MHC *DRB* class II diversity in a long-term study population of mountain goats (*Oreamnos americanus*) at Caw Ridge, Alberta, and two other populations from British Columbia, Canada. Only two alleles were found among the three populations sampled. The Caw Ridge population was fixed for one of the two MHC *DRB* alleles, but this lack of variation did not appear to have affected it negatively because the population doubled over two decades and had no history of any apparent infectious diseases. Past population bottlenecks during Pleistocene glaciations are thought to have been the main factor contributing to the low levels of MHC diversity in mountain goats, a hypothesis supported by our previous work reporting low polymorphism at neutral loci. Additionally, the limited MHC variability in mountain goats may be related to its northern distribution as we found that allelic diversity at MHC *DRB* class II in wild ungulates decreases with increasing latitude, possibly as a result of low parasite diversity at high latitudes. The low MHC variation in mountain goats and other northern ungulates such as muskoxen (*Ovibos moschatus*) may expose these species to population outbreaks that could be generated by introduced pathogens or northward shifts in the distribution of pathogens with global climate warming.

Keywords Genetic drift · Latitude · Major histocompatibility complex (MHC) · Pathogens and parasites · Wild ungulates

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Introduction

In vertebrates, the major histocompatibility complex (MHC) plays a central role in foreign antigen recognition and immune response to pathogens and parasites (Klein 1986; Hedrick 1994; Bernatchez and Landry 2003; Piertney and Oliver 2006). High levels of allelic diversity have been found in this group of closely-linked genes with >350 alleles observed at a single MHC locus (Robinson et al. 2003). This variation is thought to be maintained through parasite-mediated balancing selection (Edwards and Hedrick 1998) and an increasing number of studies support this evolutionary force as a promoter of MHC diversity in vertebrates in both captive (Arkush et al. 2002) and wild species (Harf and Sommer 2005). Thus, MHC polymorphism is expected to confer higher individual resistance to infectious diseases, such that populations showing low levels of MHC variation are expected to be more susceptible to detrimental pathogens and parasites (O'Brien and Evermann 1988) and demographic decline (Lochmiller 1996). Hence, some populations known to have decreased in numbers due to

infectious diseases have been investigated for potentially low MHC diversity under these expectations (Gutierrez-Espeleta et al. 2001).

Past population bottlenecks, according to their incidence and level, can lead to limited MHC diversity and increase species vulnerability such as was reported in the cheetah (*Acynonyx jubatus*, O'Brien et al. 1985). Many other endangered species exhibit low MHC polymorphism and are known to have gone through severe population bottlenecks (Hedrick et al. 1999, 2000a, b; Blankenburg et al. 2003). However, some species persist and do well despite low MHC polymorphism or even monomorphism caused by past population bottlenecks (Mikko and Andersson 1995; Mikko et al. 1999), including some of anthropic origin (Ellegren et al. 1993; Weber et al. 2004). On the other hand, other species have maintained moderate to high variability at the MHC despite severe population bottlenecks, likely through balancing selection (Wenink et al. 1998; Aguilar et al. 2004). A species demographic history (Yuhki and O'Brien 1990) and parasite-based balancing selection (Edwards and Hedrick 1998) may therefore play major roles in shaping MHC variation (Bernatchez and Landry 2003; Piertney and Oliver 2006).

It has been proposed that restricted MHC variability can also originate from factors related to species' social organisation such as solitary lifestyle (Ellegren et al. 1996) or monogamous mating system (Sommer et al. 2002) where few intraspecific contacts and therefore low possibilities of infectious diseases transmission would favour low MHC polymorphism. In marine mammals, a decreased exposure to pathogens and parasites due to the environment in which they occur has also been suggested as a potential cause of the low MHC variation reported in these species when compared to terrestrial mammals (Trowsdale et al. 1989; Slade 1992; Murray et al. 1995; but see Hoelzel et al. 1999; Lehman et al. 2004). Similarly, in terrestrial mammals Van Den Bussche et al. (1999, 2002) proposed that Arctic ungulate species may be exposed to fewer pathogens and parasites than those living close to the equator and thus, MHC diversity would be lower in northern ungulates compared to those at lower latitudes.

Here, we investigated MHC *DRB* exon 2 variability in a long-term study population of mountain goats (*Oreamnos americanus*) and two other wild populations. In the long-term study population, we examined the relationship between MHC *DRB* allelic diversity and demographic growth and how it influenced the prevalence of apparent infectious diseases. In addition, we tested Van Den Bussche et al.'s hypothesis (1999, 2002) and assessed whether MHC *DRB* exon 2 diversity in mountain goats could be linked to their latitudinal distribution by comparing it to the MHC diversity of other wild ungulates distributed between the equator and the North Pole. Mountain goats are distributed mainly in the Rocky Mountains of Canada and northern USA as well as the western coastal ranges of British Columbia and southern Alaska (Côté and Festa-Bianchet 2003). They are thought to have come from Asia, crossing the Bering Land Bridge between Siberia and Alaska during the Pleistocene and colonising the mountains during the glaciations (Côté and Festa-Bianchet 2003). Because of a likely history of past population bottlenecks during Pleistocene glaciations, we hypothesised that mountain goats could exhibit low levels of MHC variation. This hypothesis was supported partly by our previous work reporting monomorphism at many (57%) neutral genetic markers ($n = 68$) in the long-term study population (Mainguy et al. 2005), including the locus OMHC1 located within the MHC *DRB* class I region in domestic sheep (*Ovis aries*, Crawford et al. 1995).

Methods

Studied population

The Caw Ridge mountain goat population, Alberta, Canada (54°N, 119°W), has been intensively monitored since 1990. Individuals are captured in remotely-controlled box traps baited with salt, chemically immobilised and marked with plastic ear tags and canvas collars (Côté et al. 1998). A disc of ear skin has been collected from every goat captured since 1994 for genetic analyses. Signs of apparent diseases or ectoparasites were noted during captures. Nearly all individuals within the population are marked (98% of goats aged ≥1 year old since 1993) and observed daily from May to September each year, providing accurate counts of population size (Hamel et al. 2006).

Genetic analyses

We randomly selected 14 individuals from the Caw Ridge population to sequence a 249-bp fragment of the MHC *DRB* exon 2, the most polymorphic class II gene in cattle (Andersson et al. 1991) and one of the most polymorphic in humans (Robinson et al. 2003). Tissues were also obtained from two populations in British Columbia: Glacier National Park (51°N, 117°W; $n = 5$), and near Fort St. John (56°N, 121°W; $n = 6$) to investigate allelic diversity at the species level although

the populations sampled did not cover the entire species' range. Total genomic DNA from muscle or skin tissues was extracted using a QIAGEN DNeasy® kit according to the manufacturer's protocol.

Major histocompatibility complex *DRB* exon 2 was amplified using LA31-K and LA32-K primers previously designed to optimise amplification in thinhorn sheep (*Ovis dalli*, Worley et al. 2006). These primers are a shortened version of those of Sigurdardóttir et al. (1991) designed for cattle and that have been used successfully in many ungulates (Mikko et al. 1999). Each 10 µl polymerase chain reaction (PCR) contained PCR buffer, 2 µl of DNA template, 1.5 mM $MgCl_2$, 0.16 mM of each dNTP, 40 µM of each primer and 0.5 U of Bio*Taq* DNA polymerase (Bioline). Amplifications were performed with the following temperature profiles: 94°C for 3 min, 35 cycles at 94°C for 30 s, 55°C for 30 s, and 72°C for 45 s, followed by a 5-min extension at 72°C. PCR products were purified on a 1.5% agarose gel and the band corresponding to the amplified product isolated with QIAGEN QIAquick Gel Extraction® kit according to the manufacturer's protocol. Sequences of the purified PCR products were run on an ABI 3730 automatic sequencer using BigDye Terminator Cycle Sequencing Ready Reaction kit (Applied Biosystems).

MHC variability and latitude in wild ungulates

We tested for a relationship between the total number of MHC *DRB* exon 2 alleles reported in the literature in wild ungulates of the Northern Hemisphere and their latitudinal distribution using a generalised linear model with Poisson error structure and the backwise procedure for model selection. For each species, the number of individuals sequenced and the number of populations sampled were included as covariates to control for unequal sample sizes. Populations were assigned to the nearest latitudinal degree according to the literature and the Oxford Atlas of the World (2001). The latitude assigned to a species was the mean of the locations reported for that species weighted by the number of individuals sampled at each location and therefore rarely covered the entire species' range. When information on the samples' origin was limited (for six species), we either used the mid-point between the northern and southern limits of the locations reported or of the species' range according to Feldhamer et al. (2003, North America) or Mitchell-Jones et al. (1999, Europe). Therefore, as the latitude assigned to a species represents either a part of their range (e.g., for bighorn sheep *Ovis canadensis*, Gutierrez-Espeleta et al. 2001) or an approximated location (e.g., for muskox *Ovibos moschatus*, Mikko et al. 1999) which could potentially introduce a bias, the relation we examined can only be regarded as a broad exploration of a pattern based on all available information.

Results

MHC diversity in mountain goats

Only two alleles were found in the three populations investigated. A unique allele was found in the Caw Ridge population (*Oram-DRB*01*, GenBank accession number: DQ648492). We estimate that the probability of failing to detect a rare allele at frequency of 0.05 in our sample of 28 sequenced alleles was $(1–0.05)^{28} = 0.238$, which corresponds to a power of 76.2%. Individuals from Glacier National Park had the same fixed genotype, whilst those from the Fort St. John region had two alleles, of which one was identical to Caw Ridge and Glacier National Park. The second allele (*Oram-DRB*02*, GenBank accession number: DQ648493) differed only by a single nucleotide polymorphism in codon 78 that was not synonymous, changing the amino acid glycine (*Oram-DRB*01*) for valine. *Oram-DRB* allelic frequencies per population are shown in Table 1.

Population growth and infectious diseases

The Caw Ridge mountain goat population expanded from 81 individuals in 1990 to 156 in 2006 ($\lambda = 1.60$; Fig. 1). Three hundred and seventy-six individuals have been captured one to eight times at our study site for a total of 665 captures. Despite this large number of captures, no signs of apparent debilitating infectious diseases have ever been observed, although very few individuals (<1%) were found to be infected with Rocky Mountain wood ticks (*Dermacentor andersoni*). Eight individuals found dead in our study area have also been necropsied by a veterinarian and were free of diseases.

Table 1 Frequency of *Oram-DRB* alleles of the MHC *DRB* class II occurring in three populations of mountain goats

Alleles	Caw Ridge (Alberta)	Glacier National Park (British Columbia)	Fort St. John (British Columbia)
*Oram-DRB*01*	1.000	1.000	0.750
*Oram-DRB*02*	0.000	0.000	0.250
n	28	10	12

n = number of chromosomes examined per population

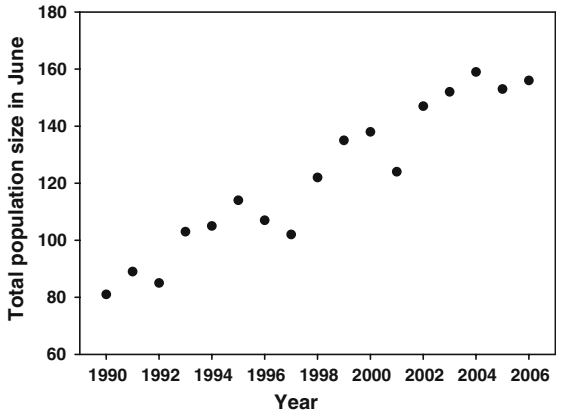

Fig. 1 Total number of mountain goats in June in the Caw Ridge population, Alberta, Canada, 1990–2006

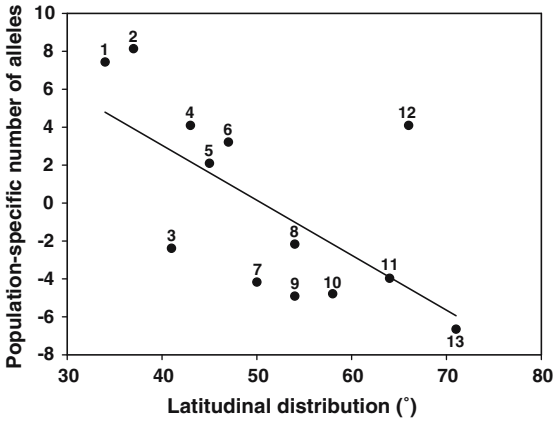

Fig. 2 Relationship between MHC *DRB* exon 2 allelic diversity corrected for the number of populations sampled (i.e., the residuals of the relation between number of alleles and number of populations sampled) and latitudinal distribution in wild ungulates of the Northern Hemisphere. (1) Bighorn sheep *Ovis canadensis*, Gutierrez-Espeleta et al. (2001); (2) White-tailed deer *Odocoileus virginianus*, Van Den Bussche et al. (2002); (3) Spanish ibex *Capra pyrenaica*, Amills et al. (2004); (4) Pyrenean chamois *Rupicapra pyrenaica*, Schaschl et al. (2005); (5) American bison *Bison bison*, Mikko et al. (1997); (6) Alpine chamois *R. rupicapra*, Schaschl et al. (2004); (7) Fallow deer *Dama dama*, (8) Roe deer *Capreolus capreolus*, (Mikko et al. 1999); (9) Mountain goat *Oreamnos americanus*, this study; (10) Moose *Alces alces*, Mikko and Andersson (1995), Mikko et al. (1999); (11) Thinhorn sheep *Ovis dalli*, Worley et al. (2006); (12) Reindeer *Rangifer tarandus*, (13) Muskox *Ovibos moschatus*, Mikko et al. (1999)

MHC variability and latitude in wild ungulates

Information on MHC *DRB* exon 2 diversity has been reported for 13 wild ungulate species distributed in the Northern Hemisphere. Number of individuals sequenced per species did not influence the number of alleles found ($F_{1,9} = 0.14$, $P = 0.71$), but the number of populations documented did ($F_{1,10} = 11.7$, $P = 0.006$). After accounting for the effect of the number of populations sampled, MHC *DRB* exon 2 allelic diversity decreased with increasing latitude ($F_{1,10} = 6.54$, $P = 0.03$; Fig. 2). However, to take into consideration the possibility that one species might have disproportionately influenced the relationship, we reran the analyses 13 times by excluding a different species each time. In 9 out of 13 analyses (69%), the relationship remained significant ($0.001 < P's < 0.05$), whereas in the 4 others, the relationship was near significance level ($0.07 < P's < 0.08$).

Discussion

The number of MHC *DRB* class II alleles in the three populations of mountain goats studied is low and comparable to those reported amongst species known to have gone through population bottlenecks (Hedrick et al. 1999, 2000a, b; Sommer et al. 2002; Blankenburg et al. 2003; Drake et al. 2004; Babik et al. 2005; Wan et al. 2006). The low genetic diversity in mountain goats could be largely attributable to Pleistocene glaciations as has been suggested in other ungulates (Mikko et al. 1999; Loehr et al. 2006), where depletion of the gene pool would have occurred via the combined actions of inbreeding and genetic drift. Furthermore, mountain goats tend to exist in islands of habitat with limited gene flow between populations (Côté and Festa-Bianchet 2003). As such, the eroding effects of inbreeding and drift on genetic variability are expected to persist due to strong population structure, a specific aspect of the demography and life-history of mountain ungulates (e.g., Amills et al. 2004; Worley et al. 2006). Different alleles, however, could be fixed or lost in different populations (Babik et al. 2005). Interestingly, the same allele was found among the three populations sampled which were 250–575 km apart. Thus, the allele *Oram-DRB*01* may represent an optimum haplotype in this species (Visscher et al. 2001). Altogether, our previous findings on neutral markers (Mainguy et al. 2005) combined with the low MHC variability found in this study suggest that mountain goats exhibit low levels of genetic variability.

Despite apparent monomorphism at one of the most variable MHC locus reported in mammals, the Caw Ridge mountain goat population has continued to increase and has shown no signs of severe infectious diseases. This is in line with previous studies reporting that muskox, northern elephant seal (*Mirounga angustirostris*) and Eurasian beaver (*Castor fiber*) populations, for instance, have expanded in the last

century despite being monomorphic at the same MHC *DRB* exon 2 gene (Mikko et al. 1999; Weber et al. 2004; Babik et al. 2005). The demographic doubling of the Caw Ridge population in the last 15 years may partly be attributable to the possible absence of severe debilitating pathogens and parasistes or, alternatively, to weak selection on MHC loci (Klein et al. 1993) as was suggested in other northern ungulates (Mikko et al. 1999). However, because we used only one locus, we cannot rule out the possibility that other MHC loci might have been polymorphic in the Caw Ridge population, or that we have missed some rare alleles (i.e., present at <5% in the population) at the studied locus. On the other hand, the low genetic variation we found at the *DRB* locus should be correlated with genetic variation at other class II genes since these loci are in strong linkage disequilibrium, at least in humans (Marsh et al. 2000).

Interspecific data suggest that latitude may influence MHC *DRB* variability in wild ungulates through a plausible relation between MHC and pathogen diversity. Recently, the richness of human parasitic and infectious diseases has been reported to decrease from equator to poles (Guernier et al. 2004), whilst levels of MHC polymorphism has been found to increase with pathogen diversity in humans (Prugnolle et al. 2005) and wild fish species (Wegner et al. 2003; Šimková et al. 2006). It is therefore possible that an indirect relationship exists between MHC diversity and latitude in ungulates. This finding, however, should be viewed with caution due to several limitations. For one, the species compared in Fig. 2 have experienced different demographic histories (e.g., American bison *Bison bison* that experienced a sharp decline, Mikko et al. 1997) and average effective population sizes. Phylogenetic distances within the order Artiodactyla could also reasonably be expected to influence allelic diversity. However, we found that MHC *DRB* allelic diversity was lower in northern than in southern ungulates, supporting the hypothesis of Van Den Bussche et al. (1999, 2002). This trend could be the result of a low selection pressure of pathogens and parasites on MHC polymorphism at high latitudes. The presence of a high number of alleles in reindeer (*Rangifer tarandus*), despite its northerly latitudinal distribution (see Fig. 2), suggests, however, that other mechanisms are also shaping MHC variability in ungulates, although *Rangifer* is known to generally exhibit more genetic variability than other cervids (Côté et al. 2002). In other mammalian species such as pinnipeds, high levels of MHC variability have also been reported at extreme latitudes (Hoelzel et al. 1999; Lehman et al. 2004), suggesting once again that parasite-based balancing selection and population bottlenecks are not the sole factors influencing MHC polymorphism.

There may be other explanations for the relationship between latitude and MHC allelic diversity. For instance, harsh climate at high latitudes could reduce genetic variability by negatively affecting individual survival and thus reducing both effective population size and the species' potential to maintain high genetic diversity or to restore it when it is lost. Alternatively, and not mutually exclusive of the previous hypothesis, post-Pleistocene expansion could yield a similar pattern of decreasing MHC variation, as genetic diversity often decreases with increasing latitude within a species following recolonisation (Galbreath and Cook 2004; Prugnolle et al. 2005). Genetic drift could therefore outweigh balancing selection in shaping MHC variation (Miller and Lambert 2004; Campos et al. 2006), although Prugnolle et al. (2005) recently shown that local pathogen richness amongst human populations distributed worldwide explained a significant part of the variance in human leukocyte antigen (HLA; known as MHC in other vertebrates) class I diversity when accounting for colonisation history. A more appropriate approach to test the effect of latitude on MHC diversity would thus be to control for genetic drift. This could not be done in our study as no standard set of markers was available to compare MHC and neutral loci to disentangle the potential effects of parasite-based selection from those of genetic drift amongst species. A more rigorous test of the relationship between latitude and MHC diversity could be conducted within a species with a broad latitudinal distribution. One could then account for neutral evolutionary forces (e.g., in simultaneously genotyping individuals at microsatellite loci) and eliminate this potential confounding factor as well as different demographic and phylogeographic histories between species. For instance, white-tailed deer (*Odocoileus virginianus*), whose range covers >50° of latitude (Feldhamer et al. 2003) and for which MHC *DRB* alleles have been identified in relation to pathogen resistance (Ditchkoff et al. 2005), would be an interesting model species in which to further elucidate the factors shaping mammalian MHC diversity and its influence on disease susceptibility and population dynamics.

Overall, we showed that mountain goats exhibit low levels of genetic variability, possibly stemming from bottlenecks experienced during the Pleistocene glaciations. The lack of severe epidemics in mountain goats (Côté and Festa-Bianchet 2003) may result from its northern and high altitude distribution where few

pathogens and parasites may prevail. In addition, the low MHC variability in mountain goats does not seem to negatively affect its demography based on the Caw Ridge population. However, mountain goats, and other northern ungulates exhibiting limited MHC polymorphism, may remain vulnerable to introduced pathogens and parasites, or infectious agents expending northwards with climate warming, that could potentially have significant impacts on their demography.

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