The Feline Major Histocompatibility Complex

Katrina Morris
Faculty of Veterinary Science
The University of Sydney
311 Gunn Building, B19, University of Sydney, NSW 2006 Australia
Contact: (02) 93513454, kmor9570@mail.usyd.edu.au
The author is a student enrolled in a Bachelor of Animal and Veterinary Bioscience. She is currently doing an honours project on the Major Histocompatibility Complex of the domestic cat.

The Major Histocompatibility Complex (MHC) is a region of the genome encoding genes essential to the immune system. The domestic cat MHC has been recently sequenced and analysed, which will allow for future research into the diversity and associations of feline MHC genes. This will have applications in both domestic cats and other felids such as cheetahs. The cheetah MHC is of interest to researchers due to its very low polymorphism as deduced from skin graft experimentation. This lack of MHC diversity has resulted in difficulties with breeding cheetahs in captivity. Development of MHC linked markers will enable us to determine the polymorphism of cheetah MHC alleles and will have applications in studying mating preferences. A link between mating preferences and MHC loci has been established in a range of species, but has not yet been studied in any feline species. MHC linked markers will also have applications in studying the association between particular MHC genes and feline diseases such as feline immunodeficiency virus and feline diabetes. This will have an influence on the prevention and treatment of both feline and human disease.

Keywords: Domestic cat, *Felis catus*, major histocompatibility complex, mate choice, *Acinonyx jubatus*, cheetah.

Introduction

The Major Histocompatibility Complex (MHC) is a region of the genome in all jawed vertebrates that encodes antigen presenting genes. The MHC is broadly divided into class I, class II and class III regions, though the organisation and structure of these classes differs across vertebrates. The MHC in many vertebrate species, from humans to zebrafish, has been sequenced. The domestic cat is an important species in Australia with over two million kept as pets and up to twelve million feral cats nationwide (Baldock et al., 2003). Domestic cats also play an important role as a model for human disease. Recently the MHC of the domestic cat has been sequenced and initial comparative studies have been performed revealing unique features in the domestic cat MHC (Yuhki et al., 2003, 2007). This sequencing and analysis of the cat MHC opens up potential for research into the domestic cat MHC and its associations with disease and behaviour. An association between mating preferences and MHC loci has been observed in species such as humans, mice and the three-spined stickleback (Penn, 2002, Ziegler et al., 2005). MHC associated mate choice is believed to increase the disease resistance of a female's offspring (Penn, 2002, Milinski, 2006). MHC loci have also been associated with particular diseases in humans and several domestic species. These diseases include human immunodeficiency virus (Carrington and O'Brien, 2003), multiple sclerosis (Fogdell et al., 1995) and diabetes of the human (Thorsby, 1997) and dog (Kennedy et al., 2006b). However, the association of MHC alleles to mating preferences or disease susceptibility has not been investigated in the domestic cat. The aim of this review is to describe the current knowledge of the feline MHC in comparison to the MHC across vertebrate orders. This review also aims to describe the scope of knowledge of the associations of the MHC to mating preferences and disease and describe how research into these associations in felines will have implications for the breeding and management of feline species.

The Major Histocompatibility Complex

The MHC is a genomic region found in all jawed vertebrates which encodes genes essential to the innate and adaptive immune system. This is a gene dense region of the genome encoding molecules which are critical for self/nonself discrimination (Klein, 1986). These molecules, known as antigen presenting molecules, are glycoproteins whose role is to bind to foreign peptides, then present these on the outside

of the cell to be recognised by T cells (Brown et al., 1988). The MHC is divided into several regions of similar function which are the classical class I, classical class II, class III, extended class I and extended class II regions. Class I molecules are expressed on most cells of the body and consist of a heavy polypeptide chain noncovalently linked to a B2-microglobulin polypeptide (Delves, 2006). These molecules present cytosol-derived peptides to CD8+ T cells and serve as recognition elements for natural killer cells (Williams et al., 2002). One of their roles is in presenting viral peptides on the outside of a cell to mediate the destruction of virally infected cells. The class I region also encodes non-antigen presenting immune genes and non-immune 'framework' genes. The extended class I region encodes antigen presenting genes, non-immune genes and olfactory genes (Beck et al., 1999).
Class II molecules are heterodimers of α and β chains and are expressed only in specific antigen presenting cells such as macrophages and dendritic cells (Delves, 2006). These molecules present peptides generated in the vesicles of antigen presenting cells which are recognised by CD4+ T cells (Villadangos, 2001). This activates B cells to produce specific antibodies to these peptides and stimulate cytotoxic T-cell proliferation. The class II gene families in humans are the *DQ*, *DP* and *DR* gene families (Beck et al., 1999). This class also encodes non-antigen presenting immune genes such as *TAP1*, a transporter for antigen processing, and non-immune genes. The extended class II region does not contain any antigen presenting genes but encodes several immune genes including the tapasin genes (Beck et al., 1999). The class III region of the MHC encodes molecules that present antigens but contains many genes that are either directly or indirectly related to immune defence function. In humans, this includes genes coding for complement components, cytokines, tumour necrosis factor and lymphotoxin (Delves, 2006). The different class I and class II antigen presenting molecules all exhibit the same basic structure with a hydrophobic section which anchors the molecule to the membrane and a peptide binding groove (Delves, 2006). These molecules are distinguished by their differences in the peptide binding groove which allows each to present a different range of peptides to the immune system, increasing the range of peptides that can be presented to T cells. One of the remarkable features of the MHC is the high polymorphism of many of the genes encoded in this complex (Geraghty et al., 2002). For example the human class I *HLA-B* gene has over 600 allele variants identified while the human *DRB1* gene has almost 500 alleles identified (Delves, 2006). The diversity of MHC genes is likely to have arisen through pathogen driven selection and is maintained by natural and balancing selection (Klein et al., 1993).

Evolution of MHC class I and class II

One distinction between class I and class II MHC genes is in the evolutionary relationship of these genes across different orders. In the class II region there are subregions of gene families consisting of at least one pair of α and β chain genes (Yeager and Hughes, 1999). Class II genes, for example in humans and mice, contain orthologous genes as well as some genes which have undergone species-specific duplications (Kumanovics et al., 2003). The presence of these orthologous genes among distantly related mammals indicates that class II loci are likely to have evolved before the divergence of mammalian orders (Hughes and Nei, 1990). In contrast to this, orthologous relationships in class I genes are never found across orders of mammals, only between closely related species (Hughes and Nei, 1989). For example, orthologous relationships between class I genes can be seen among primates (Adams and Parham, 2001) and rodents (Ioannidu et al., 2001), but not between human and mice (Hughes and Nei, 1989). In phylogenetic analyses, class I genes from different species do not cluster together, suggesting that class I genes arise independently by gene duplication in different orders of mammals (Hughes and Nei, 1989, Kumanovics et al., 2003). This evolution of class I genes has been explained by the birth-and-death model in which new genes are created by gene duplications (Ota and Nei, 1994). Some of these duplicated genes are maintained while others are deleted or become non functional (Ota and Nei, 1994).

Comparison of MHC organisation in vertebrates

Humans and Primates

The Human MHC is located on the chromosome 6p21.3 and is known as the Human Leukocyte Antigen complex (HLA) (Beck et al., 1999). The classical MHC spans 3.6 Mbp, with the full MHC including extended class I and II regions covering 7.6 Mbp (Horton et al., 2004). The class I region contains the highly polymorphic antigen presenting genes *HLA-A*, *HLA-B* and *HLA-C* as well as various genes not related to the immune system (Beck et al., 1999). The extended class I region in humans contains the *HLA-E*, *HLA-F* and *HLA-G* genes as well as many histone and olfactory receptor genes (Beck et al., 1999). The class III region is the most gene dense region of the human genome and contains immune

gene such as complement factors, cytokines and the tumour necrosis factor (Xie et al., 2003). The area of the class III directly adjacent to the class I region encodes many genes involved in inflammation so has been referred to as the inflammatory region (Gruen and Weissman, 1997). The Class II region encodes the classical class II molecules (*DR, DQ, DP*) as well as two immune proteasome genes and *TAP* transporters which are important for efficient antigen presentation (Monaco, 1992). The extended class II region encodes mostly non-immune genes but does encode tapasin which is involved with antigen presentation (Beck et al., 1999). The MHC organisation in primates is very similar to that of humans. The largest differences between humans and other apes is the presence of a unique *HLA-A* related gene in chimpanzees (Adams et al., 2001) and differing numbers of MHC class I chain related (*MIC*) genes (Cattley et al., 1999). New world and old world monkeys show gene duplication and greater diversity in the class I region when compared with apes (Go et al., 2003, Sudbrak et al., 2003).

Eutherians

The mouse MHC is located on chromosome 17 and is similar in its organization to the human MHC. The major differences are an additional class I locus in the mouse known as the H2-K locus as well as differences in the number and sequence of class I genes (Trowsdale, 1995). The mouse has approximately 30 class I genes compared to eight in the human (Kumanovics et al., 2003). The rat MHC spans 3.8 Mbp and is located on chromosome 20. Both mice and rats lack the *MIC* genes but do have a related gene family known as the *MILL* family (Kasahara et al., 2002).
The pig MHC extends for 2.0 Mbp on chromosome 7 and encodes 152 loci. The class II region in pigs is separated from the class III and class I regions by the insertion of the centromere, which has not disturbed the gene organization or function of the MHC complex (Renard et al., 2006). The horse MHC is similar in structure and organization to the human MHC with a single contiguous gene dense MHC. However, unlike the human MHC, the *DP* gene family consists only of pseudogenes (Gustafson et al., 2003). The bovine MHC is located on chromosome 23 (Takeshima and Aida, 2006). It is divided into two subregions which are separated by about a third of the chromosome's length with the split occurring within the class II region. The class IIa subregion, which lies adjacent to the class III region, encodes the *DR* and *DQ* genes. The class IIb subregion contains the *DY*, *DM* and *DO* gene families. Cattle are missing the *DP* gene which is replaced with an additional pair of *DY* genes (Takeshima and Aida, 2006). The division of the class II genes and replacement of the *DP* genes is also seen in sheep (Liu et al., 2006).

Marsupials

The only marsupial to have its genome sequenced is the opossum *Monodelphis domestica*. The opossum MHC extends for 3.95 Mbp and contains 114 genes (Belov et al., 2006). In this species class I genes have amplified within the class II region creating a unique class I/II region (Belov et al., 2006). The position which usually encodes class I genes in eutherians is composed only of framework genes in the opossum. The class III region was found to be highly conserved between marsupials and eutherians (Belov et al., 2006). Data for species including the opossum, wallabies and echidna suggest that orthologies for class II genes can be recognised within marsupials, monotremes and eutherians, but not between these mammalian clades (Miska et al., 2002, Belov et al., 2003, Belov et al., 2006).

Birds

The chicken MHC has been described as the 'minimal essential' MHC, being smaller in size and having less genes than the MHC of mammals (Kaufman et al., 1995). The chicken MHC, also known as the B locus, is a 9.2 kb DNA sequence containing 19 genes (Kaufman et al., 1999b). The organization of the MHC is different to that in mammals with the class I genes being located between the class II and class III regions (Kaufman et al., 1999b). There are also a number of differences in gene locations. For example the tapasin gene is located in the classical class II rather than the extended class II (Frangoulis et al., 1999). The chicken also has a second MHC region on the same chromosome known as the Rfp-Y region or the Y locus. This region encodes class I and class II genes but is not involved in rapid allograft rejection (Kaufman et al., 1999a). Studies on the quail, sparrow, reed warbler and turkey show that the structure and organization of the MHC is conserved across birds (Kelley et al., 2005). However the 'minimal essential' MHC model does not appear to be consistent across birds with species including passerines, sparrows and warblers having a much larger MHCs through gene duplication (Kelley et al., 2005).

Amphibians and fish

In the frog (*Xenopus)* the organization of the MHC is similar to birds with the class III region being located between the class I and class II genes (Nonaka et al., 1997) and a structure similar to the *Y* locus occurring on the same chromosome as the MHC (Courtet et al., 2001). Only one classical class I gene exists though there are several non-classical class I genes (Flajnik et al., 1993). In the axolotl there are several classical class I sequences while there is only a single class II locus (Laurens et al., 2001). The organisation and structure of the MHC in fish is different to that in tetrapod vertebrates. In the zebrafish (*Danio rerio)* the class I, II and III regions are unlinked (Kuroda et al., 2002) and the class II region occurs in three separate groups (Bingulac-Popovic et al., 1997). Immune class III genes have not been linked to class I or class II genes in any of the species studied to date (Kelley et al., 2005). While in mammals class II genes are more conserved than class I genes, the opposite appears to be true in fish (Shum et al., 2001). In cartilaginous fish there is linkage of class I, class II and certain class III loci (Bartl and Weissman, 1994, Bartl et al., 1997). This suggests that the common ancestor of jawed vertebrates contained an organized MHC (Kelley et al., 2005).

Structure of the feline MHC

The feline MHC, also known as the Feline Leukocyte Antigen (FLA) region, has been recently sequenced and assembled using the whole-genome shotgun approach with a 1.9x sequence coverage (Pontius et al., 2007). The feline MHC spans 3.3 Mbp and is located on the domestic cat chromosome B2 (Yuhki et al., 2007). The class II, class III and the majority of the class I genes are located in the pericentromeric region of the *q* arm of chromosome B2 (Yuhki et al., 2007). The remaining class I molecules including the extended class I are located in the subtelomeric region of the *p* arm of chromosome B2 (Yuhki et al., 2007). The break in the class I region occurred in the *TRIM* gene family, specifically between *TRIM39* and *TRIM26* (Beck et al., 2005). The *p* arm of the feline B2 chromosome has undergone a chromosomal inversion, resulting in the class I genes on this arm being reversed relative to those on human chromosome 6 (Beck et al., 2005). Chromosomal rearrangements of the MHC have occurred in other mammals including a break and inversion in the bovine MHC (Takeshima, 2006) and an insertion of the centromere in the pig MHC (Renard et al., 2006).

Class I genes

The class I (classical and extended) region of the FLA spans approximately 1.8 Mbp and encodes 72 coding genes including 19 functional class I genes (Yuhki et al., 2007). Based on analysis of this class Yuhki and colleagues (2007) divided the class into three subregions (Figure 2). The proximal class I subregion extends from the *BAT1* gene which lies adjacent to the class II region, through to the *OCT3* gene. This region spans 600 Kbp and includes six class I gene fragments and eleven class I genes, three of which are predicted to be classical class I genes based on alignments with feline class I cDNA sequences (Yuhki et al., 2008). This region also includes four MHC class I related genes. The central class I subregion is assigned to the remainder of the class I genes on the *q* arm and spans approximately 800 Kbp. This region encodes 27 genes which are equivalent to framework genes in the HLA, having no antigen presenting function, and are highly conserved in comparison to the human and murine MHC. One full length class I gene and one class I gene fragment are located near the centromeric end of this region. The last subregion is the region at the subtelomeric region of the *p* arm which extends from *TRIM26* to the *OLFR* olfactory gene homologue. This region spans approximately 300 Kbp and encodes 10 framework genes but no class I genes have been identified.
In 2007 Yuhki and colleagues compared the domestic cat class I region to that of the human. In humans the region between *HTEX4* and *MOG* encodes eleven class I genes including *HLA-A*, *HLA-G* and *HLA-F* (Beck et al., 1999). In the FLA, Yuhki and colleagues (2007) demonstrated that this region has been reduced from 550 Kbp to 55 Kbp and contains no class I genes. Additionally, the human *HLA-E* gene region is missing in the FLA. In the domestic cat the *HLA-B/C* region has been greatly expanded compared to other species, with 17 class I genes in this region compared to two in the human. Also, the FLA has at least one full-length class I gene near *TRIM39* which is absent in the HLA. This gene is located at the same position as mouse genes which are believed to function as escort molecules for pheromone receptors (Loconto et al., 2003). At least four *MIC* gene homologues were also identified in the *HLA-B/C* region.

Class II genes

In 2003 Yuhki and colleagues sequenced and assessed the class II region of the FLA. The class II (classical and extended) region of the domestic cat spans 700 Kbp and encodes 44 genes, 31 of which are predicted to be expressed. This region is smaller than in the human MHC (1000 Kbp) but has a higher gene density (one gene every 17.2 Kbp compared to one gene every 18.1 Kbp). The extended and classical class II regions have conservation in the nucleotide sequence and gene organization compared with other mammalian MHCs but the structure is quite different with substantial deletions and gene duplications (Figure 1). The feline extended class II region encodes 16 genes with highly conserved sequence and a gene order identical to humans. The main difference in the extended class II region is that the three pseudogenes and one functional gene between *HSET* and *DAXX* in humans have been replaced by a single gene in the domestic cat, *RPS28*.

The classical class II region contains 28 genes, 19 of which are homologous to human MHC genes. Three genes are transposed pseudogenes homologous to human genes on other chromosomes, three genes are reverse transcriptase genes and the function of the remaining three genes has not been identified. There are four multigene segments present in the human which are absent in the FLA.

The most important of these is the deletion of the entire *DQ* gene family region which contains seven genes in humans (Beck et al., 2001). Also, the region containing *DPA1* and *DPA2* has been deleted leaving only two *DP* pseudogenes in the domestic cat. This loss of functional *DP* genes has also been seen in the equine (Gustafson et al., 2003) and bovine (Takeshima and Aida, 2006) MHC. However, the FLA is the first mammalian MHC studied to lack the entire *DQ* gene family. It is suggested that the deletion of this family has lead to the immunological tolerance and inefficient antibody induction observed in domestic cats (Yuhki et al., 2003). As a possible compensation for the lack of *DQ/DP* genes there have been duplications in the *DR* gene family. The domestic cat *DR* region has been rearranged with four gene duplications and one inversion event resulting in three functional *DRB* genes, a *DRB* pseudogene (Yuhki et al., 2008) and three *DRA* genes which do not display orthology to their human counterparts. Recently another feline haplotype containing a fifth *DRB* gene has been discovered (Yuhki et al., 2008) This compares to one *DRA* and two to five *DRB* genes in humans (Beck et al., 1999) and one *DRA* gene and three *DRB* genes in bovids (Takeshima and Aida, 2006). Like the human *DRB*, feline *DRB* is highly polymorphic. 61 *DRB* alleles were identified from a sample of 36 cats while all cats studied shared the same *DRA* alleles (Yuhki and O'Brien, 1997). However, as this study did not adopt strict criteria for allele identification, it may have overestimated allele numbers (Kennedy et al. 2002). A more recent study reported only 13 DRB alleles in a sample of 33 cats (Kennedy et al., 2002).

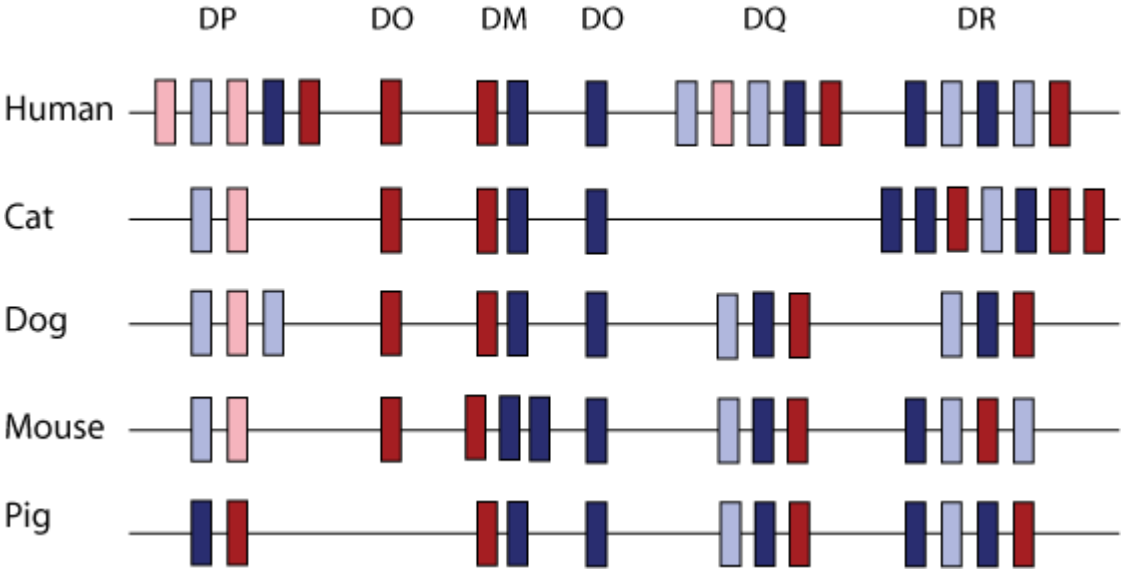

Figure 1: Ortholgous class II genes in mammals. Genes for α and β chains are represented by red and blue boxes respectively. Psuedogenes for α and β chains are represented by light red and light blue respectively.

Comparison of the canine and feline MHC

The canine MHC has been rearranged by the exact same chromosomal break between *TRIM39* and *TRIM26* as seen in the domestic cat MHC (Yuhki et al., 2007). This suggests that this chromosomal break occurred once, before the split of felines from canines which occurred approximately 55 million years ago (Murphy et al., 2001). As the split of felines and canines occurred early in the evolution of Carnivora, it has been suggested that this break in the MHC may be common to all Carnivora species (Yuhki et al., 2007). Similar G-Banding structure has been observed on the domestic cat chromosome B2 and equivalent chromosomes in other canids including domestic dog, Artic fox and Japanese raccoon dog (Nash et al., 2001, Yuhki et al., 2007). This also suggests similar chromosomal arrangements between Carnivora species. In dogs the class II, class III and class I regions are located in the pericentromeric region of chromosome 12 (Yuhki et al., 2007). Unlike in the domestic cat MHC, the remaining class I MHC are located on a separate chromosome, in the subtelomeric region of chromosome 35 (Yuhki et al., 2007). This region, as in cats, contains no class I genes. In the dog, MHC class I genes have also been found on two other chromosomes; chromosome 7 and 18 (Yuhki et al., 2007). The gene on chromosome 7 is believed to be a pseudogene while the gene on chromosome 18 is likely to encode a functional class I antigen and has a number of olfactory receptor like genes linked to it. Sequence comparisons between cat and dog MHC show that class I genes are amplified in a species-specific manner and are not orthologous (Yuhki et al., 2007). In both the dog and cat MHCs, the human *HLA-A* and *HLA-E* framework regions have been deleted and there has been an expansion of class I genes in the *HLA-B/C* region (Yuhki et al., 2007). This expansion however has not been as great in the dogs who have only 5 class I genes in this region. Unlike the cat, the dog has retained the *DQ* family with two functional genes (*DQA1* and *DQB1*) and a single pseudogene (*DQB2)* (Debenham et al., 2005). The *DR* region in the dog has not undergone the same gene duplication as in cats, with dogs possessing only two *DR* genes (*DRA1* and *DRB1*) and a pseudogene (*DRB2)* (Debenham et al., 2005). Therefore this deletion of the *DQ* gene family and expansion of the *DR* family occurred after the split of felines and canines. Similar to the domestic cats, the dog *DP* gene family only retains pseudogenes though there are three in the dog compared to two in the domestic cat (Debenham et al., 2005).

The MHC of the cheetah

The MHC of the cheetah has not been sequenced, but is of interest to researchers for several reasons. In 1985 O'Brien and colleagues (1985) performed skin allograft experiments using 14 cheetahs. They found that none of the cheetahs demonstrated rapid graft rejection of the transplanted skin tissue and only 3 out of the 14 showed slow graft rejection. As MHC antigen presenting molecules are responsible for rapid graft rejection (Snell, 1981), this indicated that the cheetahs' MHCs were identical or very similar and so were unable to distinguish foreign tissue from their own. Other studies have demonstrated using molecular genetics that the diversity of the cheetah genome is very low compared to other wild felids (Menotti-Raymond and O'Brien, 1995, Freeman et al., 2001). However, only a single study has attempted to analyse the diversity of the MHC using molecular genetic methods. Drake and colleagues (2004) used reference strand-mediated conformational analysis to assess the polymorphism of *DRB* alleles. Their results confirmed low polymorphism of cheetah MHC at this locus. However, measurement of MHC diversity across the MHC classes has not been performed. With the sequencing of the feline MHC this may be possible in the near future.

The MHC and Mate Choice

Evidence of MHC associated mate choice

Evidence for MHC disassortative mating preferences was first discovered by Yamazaki and colleagues (1976, 1978). They found that in congenic mice strains (strains that differ only in the MHC region), females were more likely to chose males that were genetically dissimilar than those that were genetically similar at MHC loci. Since this time, experimental evidence for MHC dependent mating preferences in mice has been mixed. Many studies have shown MHC dependent mate choice in both wild and laboratory mice (Yamazaki et al., 1988, Egid and Brown, 1989, Eklund, 1997), but others have found no evidence for MHC dependent mating preferences (Beauchamp et al., 1988, Eklund et al., 1991, Eklund, 1998). Penn (2002) suggests that these mixed results may be due the artificial conditions of laboratories,

insufficient sample sizes and also the fact that MHC mating preferences are likely to be subtle rather than all-or-nothing determinants.

Evidence for MHC dependent mating preferences in humans has also been contradictory. In 1995 Wedekind and colleagues showed that women preferred the body odour of men who were MHC dissimilar at *HLA-A*, *-B* and *–DR*. They also found that this preference was reversed in women taking oral contraceptives. Another study (Ober et al., 1997) found MHC disassortative mating preferences in an isolated population in North America. However several studies have found no evidence of MHC dependent mate choice in humans including a study on Amerindians (Hedrick and Black, 1997) and a study on Japanese couples (Ihara et al., 2000). These results suggest that MHC disassortative mating preferences are unlikely to be absolute or particularly strong (Penn, 2002).

Recently, strong evidence has been found for MHC dependent mate choice in fish. A study on Atlantic salmon (*Salmo salar*) (Landry et al., 2001) tested the null hypothesis that mate choice is not dependent on the MHC similarity between mates. They demonstrated that salmon choose mates to increase heterozygosity at MHC loci. They also found that in salmon mate choice was not a mechanism for inbreeding avoidance as random mating patterns were observed with regard to relatedness of individuals. The strongest evidence for MHC associated mate choice in fish has been found in the three-spined stickleback (*Gasterosteus aculeatus*). A study in 2001 (Reusch et al., 2001) found that female sticklebacks assess the odour of potential mates to deduce their MHC IIB allele number. This study found that females chose males that had a greater number of MHC IIB alleles over those with few alleles, but did not prefer males that had MHC genotypes dissimilar to their own. Aeschlimann and colleagues (2003) suggested that a female can use this information in combination with a knowledge of her own MHC polymorphism to select a mate that will complement their own set of alleles. Their study suggests that rather than always selecting males with a high number of alleles, a female's choice will be dependent on her own MHC type, so that her offspring MHC will contain an optimal number of alleles. This study was followed by a study in 2005 (Milinski et al.) who found that by adding particular stickleback peptides to the water they could predictably modify the response of females that are exposed to this water. The authors theorised that peptide ligands for MHC molecules, which reflect the MHC diversity of the individual, are the molecules which allow females to assess the MHC diversity of a prospective mate. Using this information and knowledge of her own MHC she can select a mate which will give an optimal number of alleles to her offspring. Research in the brown trout (*Salmo trutta)* (Forsberg, 2007) confirmed that females tend to choose males with an optimal number of MHC alleles, rather than the greatest number. They found that males with intermediate MHC dissimilarity produced a larger proportion of offspring than males with maximal MHC dissimilarity.

Research into MHC associated mate choice has also been performed in birds, lizards, sheep and primates. A study in 1997 (Von Schantz et al.), found that MHC was significantly associated with male spur length in the wild-ringed neck pheasant. Females prefer to mate with males with increased spur length and so this study demonstrates an example of indirect selection on the MHC in pheasants.
However, studies in the great snipe (Ekblom et al., 2004) and reed warblers (Westerdahl, 2004) found no evidence of MHC associated mate choice. This was confirmed by a study in 2005 (Richardson et al.) who also found no influence of an MHC class I locus on mate choice in warblers. However, this study did find that females were more likely to breed with alternate partners when their mate had a low MHC diversity. These studies suggest that MHC associated choice in birds may be caused by MHC type influencing the condition or appearance of the male and thus influencing female choice, rather than females choosing males that are genetically compatible. However, one recent study has found evidence that birds may select to optimise alleles. Bonneaud and colleagues (2006) found that female house sparrows excluded males with a low MHC diversity or MHC types that were too dissimilar, although further research will be needed to confirm this finding.
A study in 2006 (Lampert et al.) found no role of MHC in the mate choice of the Tungara frog. A study in Soay sheep (Paterson and Pemberton, 1997) also found no role of MHC in mate choice, though Penn (2002) suggests that this may be a result of the ability of dominant male sheep to control female preferences. A preliminary study in mate choice in sand lizards (Olsson et al., 2003) found that females preferentially associated with the odours of males that she was least related to.

Potential Functions of MHC influenced mate choice

It has been suggested that MHC disassortative mating preferences may increase resistance to parasites and disease by increasing heterozygosity of MHC loci (Potts and Wakeland, 1990). Each MHC molecule

can only bind to specific peptides and thus the more MHC alleles an individual has, the greater the range of foreign peptides an individual's cells can bind to and present to stimulate an immune response (Suri et al., 2003). As MHC disassortative mating increases the number of MHC alleles in offspring they will be able to recognize a greater range of foreign peptides and thus resist a greater range of parasites. Studies in humans have found that individuals with a high MHC heterozygosity are better able to resist hepatitis B (Thursz et al., 1997), hepatitis C (Hraber et al., 2007) and HIV (Carrington et al., 1999). However, many other studies have shown no additional resistance in MHC heterozygotes including resistance to malaria in humans (Hill et al., 1991), parasitic nematodes in feral sheep (Paterson et al., 1998) and A*eromonas* bacterium in salmon (Langefors et al., 2001). A recent study in 2007 (Ilmonen et al.) has even demonstrated reduced fitness of heterozygous mice compared to homozygous mice infected with *Salmonella.*

The exact nature of MHC associated mate choice therefore is unlikely to be explained by a need to increase MHC heterozygosity alone. It has been suggested that MHC disassortative mating preferences may have a role in maintaining MHC polymorphisms to allow species to "keep up" with rapidly evolving parasites (red queen hypothesis) (Slade and McCallum, 1992). This means that heterozygotes do not have any advantage *per se*, but that by preferring mates that either increase MHC heterozygosity or disparity of an individual's progeny, the individual is increasing its progenies' resistance to parasites (Penn, 2002). Another hypothesis is that MHC disassortative mating allows individuals to avoid kin matings which can be detrimental to their fitness (Potts et al., 1994). In fish MHC genes allow for kin recognition via odour cues (Olsen et al., 1998, , 2002) while in mice is has be found that females tend to nest with MHC similar females when siblings are unavailable (Manning et al., 1992). Research has found that females are more likely to retrieve pups when they are MHC similar (Yamazaki et al., 2000). These studies demonstrate that MHC plays a role in kin recognition and so may be an explanation for individuals selecting MHC dissimilar mates.

Selection for an optimal number of MHC alleles

Recent evidence has suggested that individuals, rather than selecting mates that are MHC dissimilar or MHC heterozygous, may select mates in order to optimise the MHC allele number of their offspring. This was demonstrated most clearly in the Miliniski and colleagues (2005) who found that MHC deficient females preferred males that were MHC diverse while the opposite was true of females with a high diversity of MHC alleles. Further to this they found that by adding peptides to the water to alter the female's perception of the male's MHC heterozygosity, they could predictably modify her response to the male. For example a female deficient in MHC alleles would become more attracted to a male also deficient in MHC if certain peptides were added to the water, while the opposite was true if both the male and female were MHC diverse. This suggests that females may use self-referencing to select a mate which will optimise rather than maximise the number of MHC alleles of her offspring (Milinski et al., 2005).

Individuals with low number of MHC alleles can present fewer peptides to T cells, so their immune system may not recognise certain pathogens (Suri et al., 2003). However, evidence suggests that very large numbers of MHC alleles are not advantageous either. Each time a new MHC molecule is added to an individual's repertoire, all T cell clones that recognize self-peptides bound to that molecule must be removed in order to maintain self tolerance (Lawlor et al., 1990). Therefore, individuals may choose mates to provide an optimal number of MHC alleles to their offspring in order to balance out the advantages of presenting an increased range of foreign peptides and the disadvantages of an increased loss of T cells (Miliniski, 2005). Further research will be required to verify this hypothesis.

Mechanism of MHC detection

The mechanism allowing animals to recognise the MHC type of potential mates is not well understood. Evidence shows that MHC genes influence odour, for example mice can be trained to distinguish odour of MHC congenic mice (Yamazaki et al., 1979, Brown et al., 1989, Penn and Potts, 1998), while studies in humans suggest that MHC type can be recognised from body odour (Wedekind et al., 1995). Yamazaki and colleagues (1983) found that mice could distinguish odours from mice who have natural deletions of class I loci. They could also distinguish some, but not all, mutants who differed at the antigen binding site of class I genes by only a few amino acids. Another study (Olsen et al., 1998) found that salmonid fish can also spontaneously recognise MHC identity. However, the molecule which mediates MHC recognition is unknown.

There are several theories as to how MHC can influence odour which have been supported by studies in mice. The potential sources of odourants include the MHC molecules themselves (Singh et al., 1987),

metabolites of MHC bound peptides (Singer et al., 1997) and microflora which are partially shaped by MHC gene products (Schellinck et al., 1991). It has also been suggested that MHC molecules may act as carriers for volatile odourants (Singh, 1998). A study (Yamazaki et al., 1999) found that trained mice could distinguish the serum odour of MHC congenic mice, but only if the serum proteins are denatured with a protease. This may suggest that MHC mediated odourants are carried in the blood and transported to the urine by a protein carrier molecule (Penn, 2002). In fish, experimental evidence demonstrates that MHC type may be detected through peptide ligands of MHC molecules (Milinski et al., 2005). Further research will be required to determine conclusively what molecule and mechanism is involved in producing an MHC typed odour and whether the mechanism is conserved among vertebrates.

MHC associated mate choice in felids

No research has currently been performed in any felid species or any carnivore species to investigate whether there is a connection between mate choice and MHC loci. This is probably due to the relatively recent sequencing of the MHC in the cat and dog and the difficulty associated with running mate choice studies with a significant sample size in these species. Research in mate choice in feral domestic cats (Ishida et al., 2001) shows that while females copulate with multiple mates during oestrous, females do not accept all copulation attempts by males showing that there is female control of paternity in domestic cats. Thus, cats may be an ideal target for extending research in MHC associated mate choice. The recent sequencing and analysis of the domestic cat MHC will enable this research to be performed more effectively. Knowledge of what influences mate preferences in felines would be useful in the design of captive breeding programs for captive felids such as cheetahs, tigers and leopards. Breeding big cats in captivity has been difficult, especially in cheetahs (Caro, 1993, Wielebnowski, 1996). In the cheetah, breeding is complicated by high juvenile mortality which is observed in both captivity and the wild (O'Brien et al., 1985, Laurenson, 1994). This high juvenile mortality is believed to be partially a result of a high level of genetic uniformity (O'Brien et al., 1985). Also, successful mating between big cats including cheetahs can be difficult (Caro, 1993). In cheetahs, this may be a result of individuals rejecting potential partners as they are genetically identical at MHC loci. By understanding what influences acceptance or rejection of a potential breeding partner in felid species we can better design breeding programs in order to build captive populations. As nearly all wild species of felidae are threatened or endangered (O'Brien and Johnson, 2005), building captive populations may be essential for the survival of felid species.

The MHC and disease

Human diseases associated with MHC loci

In humans the classical class I and class II genes have been associated with more than 100 diseases (Shiina et al., 2004). An MHC gene or region is considered to be associated with a particular disease if one or more alleles are found to be more or less common in diseased patients compared to control groups (Shiina et al., 2004). However, the molecular mechanisms for most disease associations are not well understood. The very strong linkage disequilibrium that exists between genes in the MHC makes it difficult to determine which genes, or which combination of genes, are responsible for a disease association (Horton et al., 2004). Despite this, the link between many human diseases and the MHC has now been well characterised. Diseases which have been most extensively studied for their MHC association are described below while further disease associations are summarised in Table 1. This knowledge of MHC associations could be used in the future to better understand diseases, treat patients and prevent disease.

Type 1 diabetes has been associated with alleles of *DQ* loci (Thorsby, 1997). Haplotypes which have be shown to be associated with susceptibility to type 1 diabetes include *DQA1*0301-DQB1*0302* and *DQA1*0501-DQB1*0201* (Redondo et al., 2001) while haplotypes such as *DQA1*0102-DQB1*0602* have been associated with resistance to this disease (Redondo et al., 2001). Other studies have suggested an interaction between *DQ* and *DR* loci to confer susceptibility or resistance (Yasunaga et al., 1996, Undlien et al., 1997). A class I locus, *HLA-E,* has also been associated with type 1 diabetes with the *HLA-E*0101* allele being more frequent in patients then controls (Hodgkinson et al., 2000). Type 2 diabetes has also been associated with *DR* and *DQ* loci (Li et al., 2001).

Many different MHC alleles have been found to confer resistance or susceptibility to the effects of HIV. The delay of AIDS progression has been associated with *HLA-B27* (Goulder et al., 1997) and *B57* (Migueles et al., 2000) while an acceleration of AIDS onset conferred by *B35* (Itescu et al., 1992). *HLA-B51* and *B08* may also influence susceptibility and resistance (Just, 1995). Class II genes have also been associated with HIV though the evidence has not been as strong with only small samples sizes investigated (Carrington and O'Brien, 2003). Some studies have found that the *DRB1*13* allele provides a protective effect (Chen et al., 1997) while others found it increased risk of AIDS progression (Kroner et al., 1995). In another study *DQB1*0603* and *DQB1*0201* were associated with acceleration of AIDS while *DQB1*03032* and *DQB1*04* were found to have a protective effect (Roe et al., 2000).

Multiple Sclerosis (MS), a T-cell dependent autoimmune disease, has been associated with several MHC loci. Several *DR* and *DQ* loci have been identified as a risk factor for the disease, particularly *DRB1*1501, DRB5*0101* and *DQB1*0602* (Fogdell et al., 1995). These are almost always inherited together as they are in strong linkage disequilibrium so it is difficult to determine which of these has a principle role (Fogdell et al., 1995). Lang et al. (2002) found that a T-cell receptor from an MS patient recognised myelin basic protein (MBP) restricted by *DRB1*1501*. As MBP can induce an MS-disease in susceptible rodents (Zamvil and Steinman, 1990), this further supports the hypothesis that this allele is a risk factor for the disease. MS also has an association with the myelin oligodendrocyte glycoprotein (*MOG*) gene. Research has shown that a T-cell mediated autoimmune response to the *MOG* protein plays a primary role in the pathogenesis of MS (Hemmer et al., 2002). Recent research has confirmed that MS patients express autoantibodies to native *MOG* (Zhou et al., 2006).

Table 1: Diseases with an HLA association

Disease	**Associated loci**	**Reference(s)**
HIV AIDS	*HLA-B -DR -DQ*	Carrington and O'Brien, 2003, Roe et al. 2000
Hepatitis C	*HLA-DRB1, MICA*	Yee, 2004, Karacki et al., 2004
Hepatitis B	*MICA*	Karacki et al., 2004
Type 1 Diabetes	*HLA-E –DR, -DQ*	Redondo et al., 2001, Thorsby et al. 1997, Hodgkinson et al., 2000
Type 2 Diabetes	*HLA-DR -DQ*	Li et al., 2001
Multiple Sclerosis	*MOG, HLA-DRB, DQB*	Fogdell et al., 1995, Zhou et al., 2006
Malaria	*HLA-B, HLA-DRB*	Hananantachai et al 2005, Osafo-Addo et al, 2008
Psoriasis	*PSORS1C1, PSORS1C2, HLA-C, -DRB*	Cassia et al., 2007
Rheumatoid arthritis	*MICA, AGER, HLA-DRB1*	Weyand and Goronzy, 2000
Alzheimer's	*HLA-DR*	Leon et al., 2007, Culpan et al., 1999.
Crohn's Disease	*HLA-B, -DR, TNF,*	Reinshagen et al., 1996, Kinouchi et al., 2003
Tuberculosis	*HLA-DQ, -B*	Lakshmi et al. 2006, Delgado et al., 2006

MHC associated diseases in non-human animals

MHC alleles have been associated with diseases in a wide range of animals. Identifying alleles associated with particular diseases is important in animals to treat and manage disease and in order to selectively breed for disease resistance. One of the first recognised associations between a disease and MHC loci is in Marek's disease in chickens. In 1977 it was found that chickens with the *B21* haplotype were highly resistant to the disease while those with the *B19* haplotype were highly susceptible to the disease (Briles et al.). In cattle disease susceptibility has been associated with class I loci in mastitis (Weigel et al., 1990, Rupp et al., 2007, Hameed et al., 2008) and enzootic bovine leucosis (Lewin et al., 1988), as well as class II loci in diseases including tick parasitism (Untalan et al., 2007) and Bovine Leukemia Virus (Aida, 2001). In the sheep susceptibility to both Bovine Leukemia Virus (Konnai et al., 2003) and parasitism by nematodes (Buitkamp et al., 1996, Charon et al., 2002) have been associated with alleles at the *DRB* locus. There has been much research in recent years studying the association between diseases of the dog and the MHC. Two studies have investigated the association of class II loci with diabetes mellitus. A study by Kennedy and colleagues (2006a) found that susceptibility was associated with three haplotypes which involved *DRB1, DQA1* and *DQB1* alleles. They also found that one haplotype was less common in dogs with diabetes. A second study in 2008 (Catchpole et al.) identified another haplotype involving the same loci that was associated with the disease. Another canine disease which has been associated with a class II locus is thyroiditis. Two studies have shown (Kennedy et al., 2006c, Kennedy et al., 2006d) that a

rare allele, *DLADQA1*00101*, has a significant association with hypothyroidism in a range of dog breeds. Other canine diseases with an MHC association include anal furuncolosis (Kennedy et al., 2008), immune mediated haemolytic anaemia (Kennedy et al., 2006a) and leishmaniasis (Quinnell et al., 2003). These disease associations and further diseases in other species is summarised in Table 2.

Table 2: Animal diseases with an MHC association

Species	Disease	Associated loci	References(s)
Atlantic Salmon	Furunculosis	*UBA* (class I), *DAA* (class 2)	Kjolum et al., 2008
Atlantic Salmon	Infectious anemia	*UBA, DAA*	Kjolum et al., 2006
Cattle	Lone Star Tick	*DRB1, DRB3*	Untalan et al., 2007
Cattle	Bovine Leukemia Virus	*DRB3*	Aida et al., 2001
Cattle	Clinical Mastitis	*BoLA-A2, –A11, -DR*	Weigel et al., 1990, Rupp et al., 2007, Hameed et al., 2008
Cattle	Enzootic bovine leucosis	*BoLA-A14, –A21*	Lewin et al., 1988
Chicken	Marek's Disease	*B21, B19*	Briles et al., 1977
Chicken	Cellulitis	*B-13, B-21*	Macklin et al., 2002
Dog	Diabetes Mellitus	*-DR, -DQ*	Kennedy et al., 2006a, Catchpole et al., 2008
Dog	Thyroiditis	*DQA1*	Kennedy et al., 2006b, Kennedy et al., 2006c
Dog	Anal furuncolosis	*DRB1*	Kennedy et al., 2007
Dog	Immune-mediated haemolytic anaemia	*DRB, DQA, DQB*	Kennedy et al., 2006d
Dog	Leishmaniasis	*DRB*	Quinnell et al., 2003
Sheep	Nematode/Helminth parasitism	*DRB*	Buitkamp 1996 et al., Charon et al., 2002,
Sheep	Bovine Leukemia Virus	*DRB1*	Konnai et al., 2003

Potential MHC associated diseases in felines

Only one study has been published investigating the association of a disease with MHC loci in the domestic cat. In 2004 Addie and colleagues investigated the association of feline infectious peritonitis (FIP), an immune-mediated disease caused by the feline coronavirus, with *DRB* alleles. No significant association was found between the outcome of coronavirus infection and the number of *DRB* alleles or any particular *DRB* allele. However, the authors indicate the results were complicated by breed variation and a small sample size, so an association between *DRB* alleles with FIP cannot be ruled out. With sequencing of the domestic cat genome and MHC region we are likely to see further investigation of the association of MHC loci with feline diseases. One target of this research may be feline diabetes. Extensive research has been performed in humans for type 1 and type 2 diabetes (reviewed in Thorsby et al., 1997) and preliminary research has been performed in dogs (Kennedy et al., 2006a, Catchpole et al., 2008). In both humans and dogs *DR* and *DQ* alleles are the most important for disease susceptibility in type 1 and type 2 diabetes. In domestic cats diabetes appears to have a genetic component, with Burmese cats being greater than four times more likely to have type 2 diabetes (Rand et al., 1997). The MHC association of diabetes may be different in domestic cats compared to humans as the domestic cat MHC lacks the *DQ* family. Other diseases that may have an association with the feline MHC include feline leukemia virus, feline immunodeficiency virus, feline panleukopenia and hepatitis. Understanding factors which make cats susceptible to disease is important in the prevention and treatment of diseases in cats. This is important for improving quality of life for domestic cats and for reducing the cost of preventing and treating these diseases which can be a burden on cat owners. Many of these diseases are highly prevalent in Australia, for example the prevalence of FIV in eastern Australia has been estimated at 8% (Norris et al., 2007). Furthermore, by recognising MHC alleles which are associated with susceptibility to diseases, breeders can select against individuals which have these alleles and so can improve the gene pool of a domestic cat breed. This is especially important in breeds in which particular diseases are particularly prevalent, such as diabetes in Burmese cats. Also, this research is important as domestic cats are a useful model for human disease (O'Brien and Yuhki, 1999). There are over 2 million domestic cats in Australia (Baldock et al., 2003) and veterinary research has provided a vast resource for understanding hereditary, immune and infectious disease many of which are common to humans

(O'Brien and Yuhki, 1999). By identifying MHC alleles associated to feline diseases we can assist in disease prevention in both felines and humans.

Conclusion

Sequencing, mapping and analysis of the feline MHC has revealed several unique features. In domestic cats, the *DQ* family is deleted which is the first known deletion of this family in mammalian MHCs. This deletion, along with the loss of functionality of the *DP* family leaves only a single classical class II family. This is likely to have consequences for immune functionality in domestic cats. Another interesting feature is the separation of the MHC at a breakpoint in the class I region which is shared with the canine MHC. These features are likely to have implications for future research in the domestic cat. The sequencing of the domestic cat MHC will pave the way for studying diversity and associations of the cat MHC. Development of MHC linked markers can be developed which can be used for measuring the diversity of MHC genes in the domestic cat, but are also likely to be useful in other felid species. Markers developed for the domestic cat MHC can be used to determine the polymorphism of MHC genes in the cheetah to confirm the MHC monomorphism suggested by skin graft studies. Markers may also be used to determine whether there is a significant relationship between particular MHC genes or alleles and the mate choice individual cats make. MHC associated mate preferences have been observed in a wide range of species including humans, mice and fish but have not yet been studied in cats. Determining the role of MHC in mate choice will have applications for breeding in both domestic cats and wild felids in order to help build captive populations. Lastly, sequencing of the feline MHC will enable research into the association of alleles with susceptibility or resistance to diseases including FIV, FIP and feline diabetes. This will have important applications in cat breeding and disease treatment in cats and humans as domestic cats are an important model for human diseases. The development of MHC linked markers in domestic cats will enable us to learn much about immunity, disease and behaviour in domestic cats and wild felids in the future.

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