

# RELATIONSHIP BETWEEN INBREEDING AND THE MAJOR HISTOCOMPATIBILITY COMPLEX: A REVIEW

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## ABSTRACT

Inbreeding is a phenomenon common to a number of scientific areas. In recent years, inbreeding research has focused on immunology, which is providing valuable results and broader understanding of the subject. The aim of this article was to review research of the relationship between inbreeding and the major histocompatibility complex. Though the main focus is farm animals, the results for other animal species are presented for comparison.

**Key words:** animal species; inbreeding; major histocompatibility complex

## INTRODUCTION

Discovery of the major histocompatibility complex (MHC) is playing an important role in our understanding of the function of the immune system in animals and humans. The characteristics of the MHC, in particular, high polymorphism, have also had a significant impact on other areas of research (not only immune research), such as transplantation medicine and population genetic studies. The genetic aspects of the MHC also led to research on the relationship of the MHC to a significant phenomenon in the field of animal population genetics, namely, inbreeding. The aim of this paper is to review major studies on the MHC's relationship to inbreeding, increase in homozygosity and also to some important traits, especially in relation to cattle and other farm animals. For comparison, research on other animal species is also presented.

### Inbreeding in animal populations

Animal breeding (mainly farm animals) is currently focused on a number of areas, such as

production (milk and meat), reproduction, exterior, fitness and other traits. In addition, the health of the animal plays a key role at this time too. The right combination of parent pairs is crucial for achieving optimal mating results and can confer heterosis effects to offspring (by mating of unrelated animals) or inbreeding depression (by mating of related animals). Increased inbreeding is associated with a number of adverse characteristics, including: 1). decline in quantitative traits (production, reproduction, exterior, etc.); 2). higher probability of lethal allele manifestation in a homozygous state; 3). increasing homozygosity of individual genes.

The negative effect on production, reproduction and exterior traits has been studied in great detail in recent years in relation to cattle breeding in different breeds and in various very large populations (Beller and Plesník, 1974; Kadlečík *et al.*, 2004, 2013; Sørensen *et al.*, 2005; Bezdíček *et al.*, 2005; Bezdíček *et al.*, 2012; Kasarda *et al.*, 2014; Bezdíček, 2017; Moravčíková *et al.*, 2017). Specifically, in Holstein inbred cattle ( $F_x = 9\%$ ) Thompson *et al.* (2000a) reported reduced

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Received: May 21, 2018  
Accepted: June 7, 2018

milk production by 327.6, 12.27 and 8.67 kg (milk, fat and protein in kg). In Jersey cattle, the same authors found a decline of 163.7, 8.99 and 8.16 kg (Thompson *et al.*, 2000b). Similar conclusions were drawn by Croquet *et al.* (2006), who monitored the Wallonischen Region Belgiens. In the Czech Republic, Bezdíček *et al.* (2008) studied the effect of inbreeding and reported that in cows with  $F_x = 4.0 - 12.5 \%$ , there was a reduction in milk production of 472.24 kg compared to non-inbred contemporaries. Decrease in milk production due to inbreeding was also demonstrated in a Canadian population of Holstein and Jersey cattle (Miglior 1995; Miglior 1992), similar to the Montbeliard breed (Dezetter *et al.*, 2015), Ayrshire, Guernsey, Milking-Shorthorn (Wiggans *et al.*, 1995) and other breeds. Also, crucial is monitoring at the inbreeding level in small cattle populations, where the risk of mating between relatives is greater and there is also a higher average inbreeding in the population. These studies have been conducted, for example, in Deutsches Gelbvieh and Braunvieh (Krogmeier *et al.*, 1997), in a Schweizer Braunvieh population (Casanova *et al.*, 1992) and in Pinzgau cattle in Slovakia (Kasarda and Kadlečík, 2007). E.g. in the Pinzgau cattle population in Slovakia, Kasarda and Kadlečík (2007) reported an average inbreeding coefficient of 4.225 %.

A negative effect of inbreeding on cattle reproduction has also been demonstrated. The first studies were carried out in animal husbandry (effects of inbreeding on service-period, calving interval, number of inseminations) and later on, gametogenesis (male and female) as well as embryo production. A longer service-period due to inbreeding was described, for example, by Bjelland *et al.* (2013) and Bezdíček *et al.* (2007). The effect of inbreeding on the 70-Day nonreturn rate was described by Cassell *et al.* (2003), the impact of inbreeding on calving ease and stillbirth were studied by Hinrichs and Thaller (2011) and McParland *et al.* (2007). The impact of inbreeding on ovarian activity and embryo gain after superovulation was reported by Bezdíček *et al.* (2015), Alvarez *et al.* (2005) and other authors. In particular, Bezdíček *et al.* (2015) found a higher proportion of degenerated embryos in inbred than in noninbred animals (21.48 vs. 17.54) and a higher proportion of transferable

embryos (4.29 vs. 2.72). Inbreeding depression has been studied in relation to the sperm production too. In inbred bulls ( $F_x = 10 \%$ ) a lower volume of ejaculate by 1.5 ml was found, and there was also a lower total sperm count (by  $2.4 \times 10^9$ ) and reduced sperm vitality (Maximini *et al.*, 2011).

Some authors also calculated the total financial loss associated with inbreeding in cows (Smith *et al.*, 1998; Croquet *et al.*, 2006). For estimation of inbreeding intensity an important role is also played by completeness of pedigree and the number of ancestor generations. This has been described not only in cattle (Cassell *et al.*, 2003; Lutaaya *et al.*, 1999), but also in horses (Pjontek *et al.*, 2009). An important aspect of inbreeding is its relation to genomic selection and genomic models (VanRaden, 2016) which, apart from inbreeding, include other effects (heterosis, dominance, interaction).

In addition to large (Holstein, Fleckvieh) and small populations of cattle (including Gelbvieh, Braunvieh and Pinzgauer), monitoring of inbreeding in other animal populations is important (Jafari, 2014). A valuable source of information on inbreeding is the breeding of the Przewalski and Old Kladrub horse. This is a significant genetic resource with few animals at the outset (the value of gene banks was reviewed in Chrenek *et al.*, 2017). With good animal husbandry these breeds have been successful and inbreeding was gradually reduced. In the case of the Przewalski horse, less than twenty horses were imported into Czechoslovakia in 1899-1902. This close knit animal group became the basis of today's population of about 2,000 individuals (Kůs, 2006; Jakubec *et al.*, 2012). Inbreeding in the Przewalski horse was observed in 1901-2004 with a mean value of 9.4 % (Wolc *et al.*, 2008). With progressive population growth inbreeding was reduced. The latter authors report that inbreeding of the Przewalski horse increased in particular until 1940, when its level was 37 %. During this period, it was difficult to avoid inbreeding due to the small number of animals. Increase in the population occurred in the 1960s, which was also associated with a decrease in average inbreeding in this horse population (Wolc *et al.*, 2008).

Similarly, in the Old Kladrub horse, there was a decline in inbreeding between 1993 and 2003 in stallions (from 5.65 to 5.57) and in mares

(from 7.75 to 4.88 %) as well (Jakubec *et al.*, 2009). The Old Kladrub horse and the Przewalski horse had to overcome the danger of inbreeding, especially at a time when the number of active animals was low. In general, horses are reported to be less susceptible to inbreeding depression. Tatin *et al.* (2008), for example, studied a natural herd of Przewalski's horses in France. These authors reported that the  $F_X$  coefficient for dead foals was not higher than that for living foals ( $F_X = 0.183$  vs. 0.181;  $n = 11$  vs. 51). In contrast, an effect of inbreeding on horse reproduction was found by Seving *et al.* (2004). The authors reported a partial association between incidence of retained placenta and inbreeding level in Friesian horses. Also, the impact of inbreeding on the sperm quality of stallions in the Shetland pony was investigated (Van Eldik *et al.*, 2006). The coefficient of inbreeding ranged from 0 to 25 %. The authors showed that inbreeding above 2 % was significantly associated with lower sperm motility and less proportion of morphologically normal sperm. Specifically, in the case of animals with low ( $F_X = 0-1$  %) vs. animals with high ( $F_X$  above 12 %) inbreeding there was an increase in sperm motility from 59.8 % to 67.4 %, resp. Although, less susceptibility to inbreeding was found in horses, as mentioned, overall studies have shown its negative effect on reproduction for other traits.

The negative consequences of inbreeding on a number of traits have been demonstrated in studies on various animal species. One serious consequence of inbreeding is increasing homozygosity in the entire DNA of the inbred individual. The unanswered question was, why heterozygosity was better or, oppositely, why increased homozygosity was detrimental. The answer to this question must await research findings in immunology, especially understanding of lymphocyte maturation (gene rearrangement) and the function of the major histocompatibility complex (MHC).

### **The major histocompatibility complex (MHC)**

The main function of the MHC complex in cells is the presentation of endogenous antigens to enable the immune system to recognise foreign substances. The MHC I complex has been found on nuclear cells of nearly all vertebrates. It presents the antigens from pathogens to cytotoxic

T lymphocytes (co-receptor CD8). MHC II occurs in the immune cells (e.g., monocytes, macrophages, dendritic cells, B-lymphocytes) and represents the antigen to helper T-lymphocytes (co-receptor CD4). Each individual has a specific combination of major histocompatibility complex molecules, which are inherited from the parents in a codominant manner (except for the so-called zero allele). In humans, the major histocompatibility complex is called the HLA complex (Human Leukocyte Antigens). This expresses its first appearance on leukocytes. In bovine it is called BoLA (Bovine leukocyte antigen; Fries *et al.*, 1986).

Characteristic for the major histocompatibility complex is its high polymorphism. In case of the HLA complex, the discovery of new alleles is regularly updated at the site (<http://hla.alleles.org>). For example, up to December 2017 a total of 17,695 HLA (and related) alleles (HLA I Alleles 12,893, HLA II Alleles 4,802) were described. The highest polymorphism for HLA Class I was found in genes A (genes/proteins: 4,081 / 2,853), B (4,950/3,582) and C (3,685/2,550), while in other genes (E, F, G) only several tens of alleles are known. In HLA Class II, the highest polymorphism is the DRB gene (2,440/1,779), a high polymorph is the DQB1 gene (1,178/795) too - <http://hla.alleles.org>. This very high HLA I and II polymorphism enables use of these genes for research in a number of areas.

In animals, there is an interesting database IPD-MHC (<https://www.ebi.ac.uk/ipd/mhc/>), that catalogues Major Histocompatibility Complex sequences from a number of species organized into taxonomic groups. The database was established in 2003, and in 2017 it included 7,000 alleles from 70 species (Maccari *et al.*, 2017). For example, the MHC system is reported in bovines (BoLA), equines (ELA - equine leukocyte antigen), swine (SLA - Swine Leukocyte Antigen), sheep (OLA - Ovine leukocyte antigen), in salmonid fish, felines and other animals. As noted, the major histocompatibility complex is found on nuclear cell surfaces in nearly all vertebrates. However, there are differences between animals in terms of chromosome localization (BoLA - on 23<sup>rd</sup> chromosome, SLA - on 7<sup>th</sup> chromosome, ELA - on 20<sup>th</sup> chromosome), polymorphism of individual loci, relation to disease and other factors. For example, the bovine MHC consists of three gene classes

(Class I; IIa and IIb; III.). The most studied gene is BoLA-DRB3 (Class IIa), which is highly polymorphic (Takeshima *et al.*, 2003; Miyasaka *et al.*, 2005). At present, over 130 alleles have been detected at this locus.

### Relationship of major histocompatibility complex to selected traits and inbreeding

Research on the major histocompatibility complex is generally focused on specific areas (traits), especially in relation to various diseases. The specificity of its high polymorphism in individual loci has led to MHC evaluation from the viewpoint of homo- and heterozygosity and its relation to inbreeding. Research of the MHC has been carried out around the world, in a variety of vertebrate species living in diverse conditions and in various large populations.

The *BoLA-DRB3* gene mentioned above is currently studied in cattle breeding, for example, in relation to bovine leukemia virus (BLV) disease. In particular, the *BoLA-DRB3\*0902* allele appears to be associated with this infection (Juliarena *et al.*, 2016). The authors point out that due to increase in the prevalence of BLV in a number of countries around the world and the current lack of vaccine or treatment, a viable strategy is the selection of infected cattle carrying the *BoLA-DRB3\*0902* allele (Juliarena *et al.*, 2016; 2017). Association between *BoLA-DRB3* and embryonic mortality during *in vitro* fertilization was studied by Kulaj *et al.* (2015). In Holstein-Friesian cattle, embryonic mortality was connected with homozygosity at the *Bola-DRB3* locus. The *BoLA-DRB3* gene was also examined in relation to resistance to mastitis and somatic cell count in cattle (Rupp *et al.*, 2007; Nandedkar *et al.*, 2017; Sharif *et al.*, 2000; Starkenburg *et al.*, 1997). The relation of mastitis and the major histocompatibility complex in cattle was evaluated in relation to the gene *BoLA-DQA* (Takeshima *et al.*, 2008) in cattle as well. In this study, homozygous *BoLA-DQA1\*0101/0101* and *BoLA-DQA1\*10011/10011* genotypes were found to be associated with higher susceptibility to mastitis in cows, caused by *Streptococci* and *Escherichia*, respectively. The authors conclude that heterozygosity of the *BoLA-DQA1* gene is connected with resistance to mastitis in cows (Takeshima *et al.*, 2008). Similarly, in sheep, Hui *et al.* (2012) showed that polymorphism in MHC-

DQB1 may be connected with immune protection. The polymorphism was assessed in Chinese Merino sheep and the authors found a relation of this gene to *Cystic echinococcosis* disease. In the Suffolk breed, Sayers *et al.* (2005) identified seven alleles in the Ovar-DRB1 gene and also found that this gene plays a major role in resistance to sheep nematode infection. An important association of the MHC class II DRB1 gene was found with resistance to two chronic respiratory diseases in sheep - Ovine pulmonary adenocarcinoma and Maedi-Visna (Larruskain *et al.*, 2010). The major histocompatibility complex in sheep was the focus of one review aimed at genetic and epigenetic factors influencing mastitis in ewes (Tančin *et al.*, 2016).

The advantages of heterozygosity (MHC genetic diversity) have likewise been demonstrated. For example, Agudo *et al.* (2012) found a positive correlation between genetic diversity in MHC in birds and breeding fitness. In fish (Atlantic salmon) increase in heterozygosity in offspring was shown by the preference for mating between fish with dissimilar MHCs (reviewed by Bernatchez and Landry, 2003; Landry and Bernatchez, 2001).

In addition to MHC research, from the standpoint of different traits and the advantages of heterozygosity, a number of studies have focused on inbreeding and mating between related animals. Some key experiments were carried out in mice. In one study, the rationale was that it is an attempt to select a partner according to different MHCs, thereby avoiding inbreeding (Potts *et al.*, 1991; Yamazaki *et al.*, 1976). Demonstration of the importance of MHC was also found in laboratory *in vitro* fertilization procedures with two inbred mouse strains (Wedekind *et al.*, 1996). In addition to the MHC, mouse research has also focused on major urinary proteins (MUP), which can be labeled by genetically-encoded pheromones and which can be applied to species behavior (Logan *et al.*, 2008; Mudge *et al.*, 2008). Studies have shown that MUP (major urinary proteins) is involved in olfactory communication in mice and that MUP profiles vary between inbred mice (Robertson *et al.*, 1996). Similar conclusions were drawn by Sherborne *et al.* (2007), who studied the relationship between inbreeding in house mice (*Mus musculus domesticus*) and two genetic factors – MHC and MUP. In their research, the authors found that there was no relation between mating in mice and MHC. However, the animals found kinship

on the basis of MUP (Sherborne *et al.*, 2007). In this context it is important to note the protein component of urine is very low in most mammals. Mice are unique in the excretion of proteins in their urine (Vandenbergh *et al.*, 1975).

Inbreeding avoidance through MHC has been observed in non-human primates. One interesting study was performed by Schwensow *et al.* (2008a; 2008b). These authors evaluated the role of MHC diversity in terms of choice of mate in a promiscuous primate (mouse lemur – *Microcebus murinus*) and in an obligate pair-living primate (dwarf lemur – *Cheirogaleus medius*). They found that in mating, promiscuous primate males with dissimilar MHC were preferred for fertilisation. In non-humans primates this was the first study showing the importance of the MHC in post-copulatory mate choice (Schwensow *et al.*, 2008a). In another study, the same authors focused on an obligate pair-living primate. The importance of MHC-genes for mate choice and partner selection was confirmed. Females preferred males who would guarantee higher heterozygosity and larger number of MHC-alleles in their offspring (Schwensow *et al.*, 2008b).

The major histocompatibility complex has been studied by a number of authors in horses including the Przewalski (Hedrick *et al.*, 1999) and in Old Kladrub horses (Hořín *et al.*, 1998; Janova *et al.*, 2013), in donkey (Arbanasić *et al.*, 2013) and in a plains zebra population (Kamath and Getz, 2012). Most papers focused on polymorphism of the major histocompatibility complex and its relation to the selected traits. Some researchers also studied inbreeding avoidance in horse. Duncan *et al.* (1984) found that by random mating in a natural (isolated) herd of Camargue horses the inbreeding coefficient was lower than expected according to random mating. There was also reduced sexual behaviour with members of their own harem. Regarding an involvement of the MHC in female choice, Burger *et al.* (2010) found interesting results from monitoring 19 mares aged 5-17 years (different breeds). They found a tendency ( $P < 0.063$ ) for estrous mares to select stallions with a different major histocompatibility complex (ELA). All ovulations in the mares in this test were induced by 1500 IU hCG i.v. In another study, Andersson *et al.* (2012) focused on the relationship between MHC II and insect bite hypersensitivity (a serious chronic allergic dermatitis in horse).

They found that homozygosity in MHC II was connected with a greater danger of developing this disease.

An important source of information on inbreeding and MHC research is specific animal populations such as bottleneck populations. For example, O'Brien and Evermann (1985; 1988) reported that the Cheetah population (*Acinonyx jubatus*) lost its polymorphism and is extremely genetically monomorphic, which includes its MHC genes. The authors emphasized that the loss of variability leads to increased sensitivity in the gepard population to a viral pathogen (O'Brien and Evermann, 1985).

## CONCLUSION

The studies outlined in this review confirm a substantial amount of research of the major histocompatibility complex in various vertebrate species. Although a number of relations have been found between the genes of the major histocompatibility complex and major production traits (including animal health), the influence appears in some cases to have a multifactorial character with MHC the only one of several factors.

Loss of genetic variation (for different reasons – including inbreeding), can pose a significant risk to the population or individual. In a number of studies, it has been shown that increased inbreeding is associated with decline in production, reproduction and other traits in a number of animal species (mainly in farm animals). Research in recent years also shows that inbreeding can lead to greater susceptibility to disease (weakened immunity) based on lower genetic diversity (MHC; lymphocyte receptors – TcR, BcR). In general, in the case of inbred animals there is a greater homozygosity. This corresponds to a lower number of variants in the gene rearrangement in lymphocytes (the gene rearrangement of T and B lymphocytes) and thus a lower number of antibody variants in inbred animals.

Inbreeding is generally a phenomenon that we can study at various levels in different animal species. It is also an important means for studying the biological process, especially in terms of reproduction and genetics. Research in the area of inbreeding consequences (inbreeding depression)

has made a significant contribution to a knowledge from the standpoint of the major histocompatibility complex, which is an important component of the immune system in vertebrates.

## ACKNOWLEDGEMENTS

This work was supported by the Institutional research plan MZe CR RO1218 (26.2.2018).

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