10.22059/IJVM.2022.339598.1005251

Iranian Journal of Veterinary Medicine
Volume 16- Issue 3

Review Article
Online ISSN : 2252-0554

Major Histocompatibility Complex as Marker Assisted Selection for Breeding Immunocompetent Animal

Gholamreza Nikbakht Brujeni[1]*, Pouya Houshmand[1], Atefeh Esmailnejad[2], Fatemeh Abasabadi[1]

1. *Department of Microbiology and Immunology, Faculty of Veterinary Medicine, University of Tehran, Tehran, Iran*
2. *Department of Pathobiology, School of Veterinary Medicine, Shiraz University, Shiraz, Iran*

Abstract

Due to the threat of vaccination problems and antibiotic resistance, more appropriate approaches are desired to breed disease resistance animals that are now practiced in cattle, sheep, chicken, and fish farming. Over the recent century, breeding programs based on the productive characteristics have increased animals' overall growth rate and productivity. Despite the benefits, livestock breeding with this method has caused many physiological disorders as well as a reduction in overall immunocompetence. This issue highlights the importance of genetic considerations during the process of breeding. One of the most crucial gene clusters identified in animals is the major histocompatibility complex (MHC), which plays a crucial role in the immune system to distinguishing self from non-self. Recent studies have demonstrated that some MHC regions are highly polymorphic. Also, a significant association between different MHC alleles and susceptibility/ resistance to various diseases has been found. This review summarizes the recent research on MHC polymorphism and its association with immune responses in domestic animals.

KEYWORDS: Allelic polymorphism, Immune response, Immunocompetent animal, Marker-assisted selection, MHC

Correspondence

Gholamreza Nikbakht Brujeni, Department of Microbiology and Immunology, Faculty of Veterinary Medicine, University of Tehran, Tehran, Iran. Tel: +98 (21) 61117057, Fax: +98 (21) 61117057, Email: Nikbakht@ut.ac.ir

Received: 2022-03-09

Accepted: 2022-05-10

How to Cite This Article

Nikbakht Brujeni, B ., Houshmand, P., Esmailnejad, A., Abasabadi, F. (2022). Major Histocompatibility Complex as Marker-assisted Selection for Breeding Immunocompetent Animal. *Iranian Journal of Veterinary Medicine, 16*(3), 211-227.

Introduction

During the past half-century, commercial breeding programs based on productive traits have improved animal growth rate and production. Still, high selection intensity for quantitative traits caused many physiological disorders as well as a reduction in overall immunocompetence. For breeding resistance animals, gathering knowledge regarding the population's genetic makeup is a fundamental tool that helps identify variations in immunological traits. On the other hand, knowledge of the genetic diversity at immune response genes is necessary for understanding the host-pathogen interactions, disease resistance, and susceptibility. In this regard, the combination of traditional genetic selection and molecular marker-assisted selection (MAS) based on the immunogenetics criteria is expected to be a more effective breeding approach (White & Knowles, 2013).

The major histocompatibility complex (MHC) is a cluster of genes that plays a central role in the immune system to distinguish self from non-self. It was first discovered in mice as the genetic locus responsible for rapid tissue allograft rejection and encoding some highly polymorphic alloantigens on the surface of cells. Graft rejection is an accidental consequence of the basic function of the polymorphic alloantigens, the MHC classical class I and II molecules, whose role is to bind and present peptide fragments to T lymphocytes of the immune system (Rock *et al.*, 2016; Wieczorek *et al.*, 2017; Wosen *et al.*, 2018; Nakamura *et al.*, 2019). It is now known that MHC also has important roles in autoimmunity and reproductive success. The extreme polymorphism and somatic variations in MHC genes enable the host to recognize many foreign peptides and direct immune reactions toward humoral and/or cell-mediated response (Zakharova *et al.*, 2019). T cell epitope mapping could be applied in vaccine design and formulations for all species where functional MHC molecules have been analyzed. In veterinary science, the important role of MHC in disease resistance and production traits has made it a precious marker in selection programs (Behl *et al.*, 2012; Q. H. Han *et al.*, 2019; Manlik *et al.*, 2019; Jaworska *et al.*, 2020).

Several important characteristics of MHC genes that make them exceptional candidates for investigation are mentioned in Table 1.

Table 1. Substantial properties of MHC genes that make them precious targets of research

1.	**MHC classes are polygenic**
2.	**MHC genes are the most polymorphic genes in the genome**
3.	**MHC genes are co dominantly expressed in each individual**
4.	**MHC genes play an important role in the immune system, autoimmunity, reproduction, economic traits, and life history strategies**

The MHC region, also known as leukocyte antigen (LA), comprises three clusters of genes, including classes I, II, and III. Class I and II genes express cell surface glycoproteins and are functionally divided into two types of classical and nonclassical MHC. Classical MHC molecules have polymorphic nature and present peptide ligands to T cell receptors (TcR). In contrast, nonclassical MHC molecules mediate non-restricted T cell functions such as inhibitory or activating stimuli in natural killer cells, peptide loading of class II molecules in the endosomal/lysosomal system, and displaying lipids. MHC class III encodes for other immune components like complement components (C2, C4, factor B) and cytokines (e.g., TNF-α) (Al Naqbi *et al.*, 2021; Matzaraki *et al.*, 2017; Radwan *et al.*, 2020; Tumer *et al.*, 2019).

MHC class I region includes three different loci, A/B/C, that encodes transmembrane α glycoproteins chains containing α1, α2, and mostly α3 domain, which is dimerized with soluble β-2-microglobulin. Classical MHC I molecules present endogenous antigens (e.g., viral and tumor peptides) to CD8+ T cells and mediate cellular immunity. MHC class II region includes four different loci, DP/DQ/DR/DW,

that encode alpha (α) and beta (β) chains on the surface of antigen-presenting cells (APCs). Classical MHC II molecules present exogenous antigens (e.g., bacterial peptides) to CD4+ T cells and induce effective cytokines for humoral/cell-mediated immune responses (Figure 1) (Cruz-Tapias *et al.*, 2013).

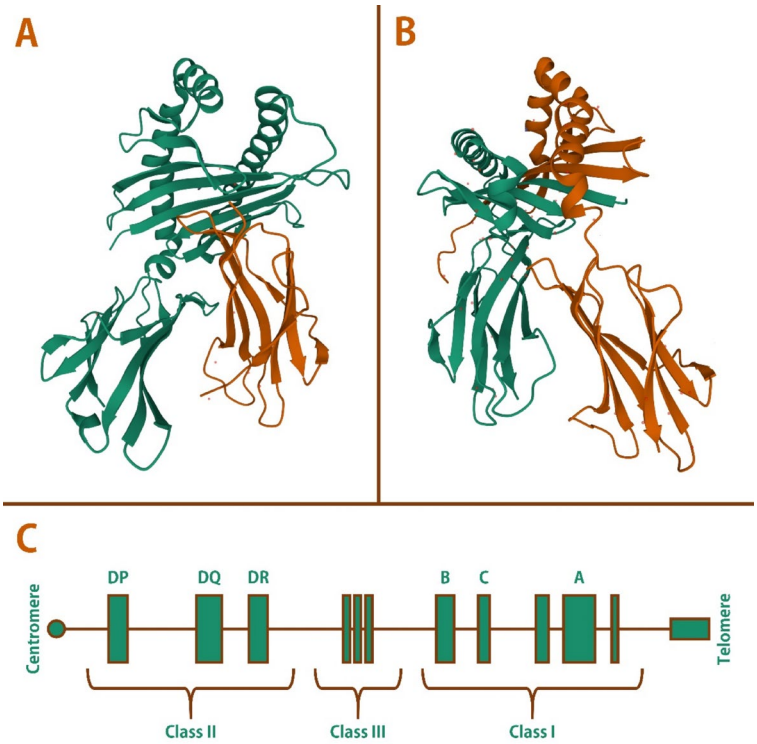

Figure 1. The three-dimensional (3D) structures and gene loci of human major histocompatibility complex (MHC). A) 3D structure of MHC class I, B) 3D structure of MHC class II, C) gene loci of MHC (Y. Li *et al.*, 2010; McMahon *et al.*, 2011; Sehnal *et al.*, 2021)

The existence of the MHC system in different species was initially found as leukocyte antigens. Lymphocyte immunizations and the generation of monospecific antibodies against lymphocytes were commonly used for identifying the MHC haplotypes. Serological typing has several limitations, including the presence of highly similar MHC epitopes, the existence of novel haplotypes in a different population, variability of non-MHC antigens, and subjectivity in the interpretation of serological reactions (Janet E. Fulton *et al.*, 2006).

Several molecular methods are now available to analyze MHC alleles and genotypes in domestic animals. Some of the PCR-based methods that are available for specified loci are sequence-specific primers (SSP), sequence-specific oligonucleotide probe analysis (SSOP), and single-strand conformational polymorphism (SSCP), restriction fragment length polymorphism (RFLP) analysis with identification by Southern blot analysis (Nikbakht *et al.*, 2009). Direct DNA sequencing or cloning and sequencing the PCR products are the gold standard for most phylogenetic studies. However, the cost required for such analysis is relatively high and time-consuming. The MHC haplotypes will be determined using a microsatellite marker located within the MHC region. This approach has successfully been used for cattle and chicken (Abdurakhmonov, 2016; Janet E. Fulton *et al.*, 2016; Iglesias *et al.*, 2019; Manjula *et al.*, 2021; Gholamreza Nikbakht *et al.*, 2013).

The polymorphic nature of the classical MHC molecules is reflected by the high number of alleles detected for each locus. In most vertebrate species, a high degree of genetic polymorphism has been reported in the MHC II region. In this region, the DR locus is highly polymorphic and probably plays an essential role in developing MHC-restricted immune responses. The MHC class II alleles have also been

associated with many immune and non-immune responses in humans and animals. They are considered a genetic risk factor for many autoimmune diseases. This review summarizes our findings over two decades of intense research on MHC polymorphism and its associations with immune responses in domestic animals.

Ruminants

Cattle

In cattle, the MHC system, called bovine leukocyte antigens (BoLA), was initially found by serological methods via lymphocyte immunizations and by the generation of monospecific antibodies. BoLA is located on chromosome 23 and contains about 154 predicted functional genes (Behl *et al.*, 2012). Class I genes are composed of two BoLA-A and BoLA-B regions. Only the BoLA-A locus seems to be functional, with nearly 100 known classical alleles listed on the Immuno Polymorphism Database (IPD) (https://www.ebi.ac.uk/ipd/mhc/group/BoLA/) (Figure 2).

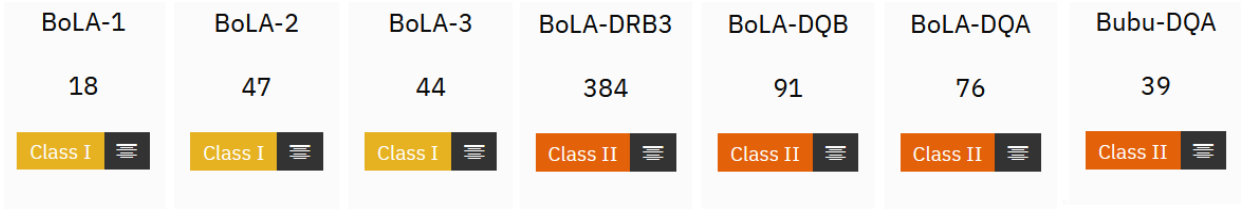

Figure 2. Alleles of different regions of bovine leukocyte antigen (BoLA)

Class II genes are located in two separated subregions, IIa and IIb. The IIa comprises two gene clusters, DR and DQ (not DP gene), that express one DR molecule and one or two DQ molecules. Cattle have one monomorphic coding gene for α chain of the DR (DRA) and three genes that encode for the β chain of the DR (DRB 1-3) molecule. DRB1 is a pseudogene, DRB2 is poorly expressed, but DRB3 is strongly expressed. DRB3 is the most polymorphic locus for which, to date, 384 alleles have been identified (Figure 2). The DQ genes are composed of DQA (DQA 1–5) and DQB (DQB 1–5) genes, with at least 76 BoLA DQA and 91 BoLA DQB alleles. DR and DQ molecules are mainly involved in presenting a broad spectrum of antigens in cattle. The BoLA class IIb locus contains genes involved in antigen processing and transport (TAP) (Giovambattista *et al.*, 2020; Kumari *et al.*, 2021).

There is limited knowledge on variability, structure, interspecies phylogeny, and phylogenetic characteristics of cattle MHC. We have performed several projects on exon2 of BoLA-DRB3 (BoLA-DRB3.2) allelic polymorphism among Holstein cattle and river buffaloes. BoLA-DRB3.2 allelic frequencies detected in Iranian cattle are summarized in Table 2 (Alkafajy *et al.*, 2020; Nikbakht Brujeni *et al.*, 2016; Ranjbar *et al.*, 2017).

The genetic diversity at BoLA-DRB3.2 was associated with the resistance/susceptibility of cattle to some infectious diseases (Table 3). In cattle, enzootic bovine leukosis (EBV) is one of the most important examples of the relationship between the MHC and infectious diseases. Nucleotide polymorphisms in the BoLA-DRB3.2 are associated with bovine leukemia virus (BLV) proviral load and different patterns of EBV, such as persistent lymphocytosis (PL) and leukemia or lymphosarcoma (LS). Specific amino acid sequences within the highly polymorphic peptide binding region of the BoLA-DRB3.2 influence the immune system's binding, orientation, and presentation. Due to the widespread of BLV, eradication programs based on the detection of BLV seropositive cattle and culling the infected animals are not feasible. In this case, breeding for disease resistance can be practiced while offering improved animal welfare and increased returns for breeders (Nikbakht Brujeni *et al.*, 2016).

Even before immune molecules (especially MHC) had been structurally characterized by experimental and in-silico methods, it was hypothesized a long time ago that areas with greater amino acid sequence variability could be considered surrogate indicators of antigen interaction points in the receptor. This general correlation has been verified (Wu & Kabat, 2008). We further analyzed the associations between MHC alleles and calf diarrhea. Calf diarrhea was significantly associated with the BoLA-DRB3.2 genotype *1104/*0101*. A potential relationship between amino acid sequences in the antigen-binding groove of BoLA-DRB3 alleles and susceptibility or resistance to calf diarrhea is demonstrated. Among twelve different DRB3 alleles, 26 polymorphic positions were detected. A significant association was identified between diarrhea and the presence of Glutamic acid and Tyrosine in pocket 4 and Valine, Glutamine, and Leucine in pocket 9 of the peptide binding region. Thus, it can be concluded that pockets 4 and 9 of the BoLA-DRB3 molecule are involved in conferring susceptibility to calf diarrhea (Nikbakht *et al.*, 2011).

Table 2. BoLA-DRB3.2 allelic frequencies detected in Iranian cattle

DRB3.2 alleles	Holstein	Sistani	DRB3.2 alleles	Holstein	Sistani
***01**	0	3.33	*24	18.75	1.67
***03**	2.52	0.67	*25	1.87	0
***06**	1.87	0	*26	1.25	0
***07**	1.87	2.67	*27	0.63	0
***08**	5.63	17.33	*28	0.63	1.33
***09**	5.63	0	*32	0.63	0.67
***10**	2.5	2.67	*33	1.87	0
***11**	2.5	7.33	*34	1.25	19.33
***12**	1.25	0	*36	1.87	0.67
***13**	1.25	0.2	*37	0	0.67
***14**	1.87	0	*39	0.63	0
***15**	3.75	15.67	*44	0	4
***16**	9.38	0	*45	0	1.33
***17**	1.25	0	*46	0	0
***20**	0.63	0	*47	0	2.33
***21**	1.25	11.33	*51	5	0
***22**	5.63	0.2	*52	1.25	0.67
***23**	7.5	0	*54	0.63	0.67

Table 3. BoLA-DRB3.2 alleles associated with resistance (R)/susceptibility (S) of cattle to infectious disease

DRB3.2 alleles	BLV	Mastitis	FMD	Parasite infestation	Theileriosis
***01**	-	-	R	-	-
***03**	S	R	R	-	-
***07**	-	-	R	-	-
***08**	S	S	-	-	-
***11**	R	R	-	-	-
***12**	-	-	S	-	-
***16**	S	-	-	-	R
***18**	S	-	S	R	-
***20**	-	-	-	R	-
***22**	S	S	-	-	-
***23**	R	S	-	-	R

DRB3.2 alleles	BLV	Mastitis	FMD	Parasite infestation	Theileriosis
⁎24	S	S	-	-	-
⁎26	-	-	-	R	-
⁎27	S	-	-	R	-
⁎28	R	-	-	-	-

Buffalo

The buffalo (*Bubalus Bubalis*) MHC genomic regions are named lymphocyte antigen (BuLA/Bubo), which have a similar overall organization to cattle (Tizard, 2018). Similarly, MHC class II genes of buffalo are located in two distinct locations but on chromosome 2p (C. Li *et al.*, 2020). MHC IIa contains DR and DQ, and IIb contains DI, DY, and DO (Medina *et al.*, 2019; Othman *et al.*, 2018). The second exons of DRB, DQA, and DQB, coding peptide binding sites (PBS) of class II molecules, are highly polymorphic. The MHC class II DRB gene in buffalo is also orthologues to the cattle DRB3 (Behl *et al.*, 2012). In buffalo, the polymorphism of DRB3 has been defined by using several PCR-based methods, including single-strand conformational polymorphism (SSCP) in Indian river buffalo, heteroduplex analysis (HA), polymerase chain reaction-restriction fragment length polymorphism (PCR-RFLP), and sequencing (De *et al.*, 2002).

Polymorphism in DRB3 exon 2 of Iranian river buffalo (Bubalus bubalis) has been analyzed. The second exon of Bubu-DRB3 was amplified by polymerase chain reaction (PCR), and polymorphisms were detected by restriction fragment length polymorphism (RFLP) and heteroduplex analysis. A series of 8 RsaI and 11 HaeIII types of the second exon based on PCR-RFLP analysis was defined, while heteroduplex analysis of the same animals showed 5 types (Ranjbar *et al.*, 2016). In different studies on BuLA-DRB3 polymorphism, some alleles were more frequent in the Holstein breed, and their frequency was between 70 to 89% (Behl *et al.*, 2012).

A quantitative measure for conservation against the variability of aligned sequences is useful for identifying sites under constraints. Various methods to quantitatively evaluate the conservation or variability of alignment sites have been developed (Johansson & Toh, 2010). Therefore, the challenge of which regions in the MHC interact with antigen in BoLA/BuLA-DRB3.2 is still an open one, and clear identification of areas of greater amino acid sequence variability is still of paramount importance.

Sheep

Although considerable effort has been devoted to identifying genetic variations at the MHC in sheep, compared to other domestic animals, Ovar is still poorly characterized (Ilhan *et al.*, 2016; Siva Subramaniam *et al.*, 2015). Several studies have demonstrated that the Ovar-DRB1 and Ovar-DQB loci can be highly polymorphic and are of great importance for understanding the host-pathogen interactions, facilitating the selection of disease-resistant animals, and accelerating the development of effective vaccines (Scott *et al.*, 1992; Sayers *et al.*, 2005; Ballingall *et al.*, 2008; Nikbakht *et al.*, 2009; Jamshidi *et al.*, 2011; Gholamreza Nikbakht *et al.*, 2012; Shen *et al.*, 2014). In the following, the results of the previous studies in this field are summarized.

The MHC gene of sheep is located on chromosome 20 and is called Ovar (Hediger *et al.*, 1991). At least six MHC class II loci in sheep are transcribed (DRB1, DRA1, DQA1, DQB1, DQA2, and DQB2). The DRB1 locus encodes highly polymorphic glycoproteins composed of α and β-subunits. The first domain of DRB1 β-subunit (β1) is similar to HLA-DR1 β1, which contains the peptide-binding site. In particular, the polymorphism is concentrated in the pockets of the antigen-binding site (Herrmann-Hoesing *et al.*, 2008).

In sheep, the polymorphism of Ovar-DRB1 has been defined using SSOP, SSCP, RFLP, DNA sequencing, and a Double Amplification Refractory Mutation System (ARMS) method, which recently has been successfully used for haplotyping (Konnai *et al.*, 2003). There are over 100 different DRB1 DNA sequences reported in GenBank. We have previously reported genetic diversity of the exon 2

Ovar-DRB1 locus by either RFLP or direct sequencing in three different Iranian fat-tailed sheep breeds: Lori-Bakhtiari (LB), Shaul (Sh), and Zandi (Za) (Table 4) (Gholamreza Nikbakht *et al.*, 2012).

Table 4. The genetic diversity of the exon 2 Ovar-DRB1 locus in Iranian fat-tailed sheep breeds

PCR RFLP types	RsaI patterns	Ovar-DRB1 alleles	New alleles		
			Allele	Most similar to Ovar-DRB1 genomic DNA type	Nucleotide identity percentage to Ovar-DRB1 genomic DNA type
1	a	*0801			
2	b	*2101			
3	c	*0702, *0803, *1202, *1701	A	DRB*1202	99%
4	d	*0805			
5	f	*0401, *0402			
6	g	*0301, *0302, *0307, *1003, *2001, *2002	B C D E	DRB*1701 DRB*1001 DRB*1101 DRB*1701	97% 99% 97% 97%
7	h	*0201, *1101, *1102	F G	DRB*0201 DRB*0102	98% 99%

Recent studies have focused on the relationship between different Ovar alleles and resistance/susceptibility to parasitic diseases. In this regard, a study demonstrated that the DRB1*1101 allele was associated with reduced egg counts and reduced IgA activity against nematode parasites in British Texel sheep (Ali *et al.*, 2019). Another study performed by Shen *et al.* revealed that Chinese Merino sheep with the genic haplotype DRB1-SacIab/DRB1-Mvalbb/DQB1- TaqIaa/DQB1-HaeIIInn were relatively resistant to cystic echinococcosis, while individuals with the genic haplotypes DRB1-Mvalbc/DQB1- Mvalyy/DQB1-TaqIab/DQB1-HaeIIImn and DRB1-Mvalbb/DQB1-Mvalcc/DQB1-TaqIab/DQB1-HaeIIImn were more susceptible (Shen *et al.*, 2014). Another factor that can discriminate resistant/susceptible individuals is the expression level of certain MHC genes. For instance, Keane *et al.* showed that the MHC class II gene Ovar-DQA1 was expressed 8.4-fold more highly in resistant sheep to the gastrointestinal nematodes than susceptible ones (Keane *et al.*, 2007).

Previous studies have not been limited to evaluating the association between Ovar alleles and parasitic diseases. For instance, in a recently published study, the association of MHC class II alleles with inflammatory cytokines and acute-phase proteins was evaluated in sheep. According to the results, allele DRB1*2101 showed a negative influence on the IL-6 response and was associated with a lower serum level of IL-6. Also, compared to the homozygotes, haptoglobin concentration was higher in DRB1.2 heterozygous individuals (Atefeh Esmailnejad *et al.*, 2021). Another research demonstrated that the DRB1*0404 haplotype was associated with increased mature weights and average daily gain in sheep, while the DRB1*0141 haplotype was associated with decreased growth (Cinar *et al.*, 2016).

Bird MHC (B Complex)

In the late 1940s, Briles described two highly polymorphic blood group systems in chickens. One of the systems, designated B, was later found to determine erythroid alloantigens and control acute allograft rejection and genetic control of the immune response to natural and synthetic Antigens. The B system of the chicken was the second major histocompatibility complex (MHC) recognized in

animals (W. E. Briles *et al.*, 1982; W. Elwood Briles & Briles, 1982).

The chicken MHC is divided between two regions of micro chromosome 16; the typical or "classical" MHC genes are located in the B complex and "non-classical genes" in the Rfp-Y region (W. E. Briles *et al.*, 1982; W. Elwood Briles & Briles, 1982). The core B complex is simple and compact, with only 19 genes in approximately 92kb, and is composed of tightly linked polymorphic regions: BF (class I) and BL (class IIβ), and BG (class IV) (Miller & Taylor, 2016; Yuan *et al.*, 2021).

There has been growing interest in genetic markers suitable for drawing population differences in qualitative and quantitative traits affecting immune responses. Besides the importance of identifying alleles in each locus, MAS for chicken has reached a precious finding on microsatellite markers located in the MHC region. Microsatellites are one of the DNA-based genetic markers that have been widely used as a standard technique for molecular genetic evaluation and mapping of a chicken's genome (Abebe *et al.*, 2015). Microsatellites (or short tandem repeats) are tandem repeat loci with a core motif of 1 to 6 base pairs repeated several times. The variations in length define the alleles at a particular microsatellite locus within a population. Because of the relative ease of identification of microsatellites, exhibiting a high level of polymorphism, random distribution throughout the genome, and a high level of heterozygosity make its application a quite significant genetic tool. Microsatellite markers are highly informative and could be used for genotyping, individual DNA identification, parentage assignment, phylogeny, population and conservation genetics, molecular epidemiology, pathology, and Quantitative trait loci (QTL) mapping. Those microsatellites that are physically located within the MHC are important for MHC typing. Though microsatellite functions in the genome have not been identified, it has been asserted that they have a linkage with some functional genes (Abdurakhmonov, 2016; Vieira *et al.*, 2016).

One of the most applicable immune microsatellite markers for chicken is LEI0258. It is a tetra-nucleotide tandem repeat that is located in the chromosome 16a region where there are genes of chicken MHC (Atefeh Esmailnejad et al., 2017; B. Han et al., 2013). An additional marker, MCW0371, is also located 10,560 bp downstream of LEI0258 in this region (Manjula *et al.*, 2021). Interestingly, LEI0258 has many alleles and an extensive range in allele sizes. These alleles are easily distinguishable using relatively inexpensive electrophoretic size separation methods. Due to its close physical location to genes of the chicken MHC, LEI0258 was investigated as a genetic indicator for B haplotypes (Manjula *et al.*, 2020; Mwambene *et al.*, 2019). MHC genes play an important role in the immune system, autoimmunity, reproduction, economic traits, and life-history strategies. Therefore, MHC typing in the poultry industry could improve breeding strategies and help speculation about its future applications. Linkage of LEI0258 microsatellite with B-F haplotype and association of these microsatellite alleles with antibody response against Newcastle disease virus vaccine and body weight as well as ectoparasite were evaluated (Mpenda *et al.*, 2020; Gholamreza Nikbakht *et al.*, 2013).

The chicken MHC is known to have a very strong association with disease resistance/susceptibility to numerous pathogens (Marek's disease virus, Rous sarcoma virus, avian leukosis virus, fowl cholera, coccidiosis, and salmonella) and autoimmune diseases, obese strain spontaneous autoimmune thyroiditis (SAT) (Silva & Gallardo, 2020; J. E. Fulton, 2020; Tizard, 2018). Our studies have shown that polymorphisms in the chicken MHC region are associated with the immune response to vaccination and productive traits (Alkaragoly *et al.*, 2018; Emam *et al.*, 2014; Gholamreza Nikbakht & Esmailnejad, 2015). Moreover, economically important traits, such as juvenile and adult mortality, body weight, fertilization rate, embryonic mortality, hatchability, sexual maturity, and egg production, are influenced by MHC genotypes (Izadi *et al.*, 2011; Lwelamira *et al.*, 2008). These characteristics of the chicken B system have made it an important subject in commercial chicken breeding programs.

Merely selection based on the productive traits of broiler chicken has caused many physiological disorders as well as a reduction in overall immunocompetence. To simultaneously improve production and fitness traits, molecular markers associated with one or both sets of traits may be useful

(Manjula *et al.*, 2021). However, in the first decade after identifying chicken MHC, several studies were performed to examine its association with production traits. Most of these studies have been done on congenic or commercial inbred lines with low polymorphism. In addition, in most of these studies, MHC typing was carried out by serology that is now replaced with molecular methods (Livant *et al.*, 2004; Martin *et al.*, 1990).

MHC association with production traits can result from various causes, including:

- Differences between B genotypes in resistance to various sub-clinical infections affecting growth and production traits.
- Interaction between MHC molecules and peptide hormone receptors active in metabolism or affecting fertility.
- Linkage disequilibrium with causative genes controlling production traits (Ewald *et al.*, 2007).

Production traits are multifactorial, controlled by a relatively large number of loci (QTLs), have low heritability, and are influenced by environmental factors. A candidate gene approach would be a powerful method for understanding the direct genetic basis involved in the expression of quantitative differences between individuals. So, we looked for a marker that doesn't have these limitations and is associated with production traits. Insulin-Like Growth Factors (IGFs) consist of a family of polypeptide hormones structurally associated with insulin with multiple metabolic and anabolic functions. IGF1 is an important regulator in stimulating growth, protein synthesis, and cell proliferation in various cell types. IGF1 polymorphism is associated with several productions and reproductive traits in poultry. They proposed that the IGF1 gene could link disequilibrium with the actual causative mutations that affect growth and carcass traits (A. Esmailnejad & Nikbakht Brujeni, 2016). Our results for the Khorasan indigenous chicken indicated significant linkage disequilibrium between LEI0258 and IGF1 loci. High MHC genetic diversity in indigenous breeds is a valuable genetic resource for associations and linkage studies (A. Esmailnejad & Nikbakht Brujeni, 2016).

Dog

The genes of canine MHC, also known as dog leukocyte antigen (DLA), are located close together on canine chromosome 12 (Niskanen *et al.*, 2016). DLA comprises three gene clusters, including class I, II, and III genes, which have a high genetic similarity to human MHC. DLA class I and II molecules are involved in presenting self and non-self-antigens to the immune cells and the regulation of immune response. In contrast, the role of DLA class III molecules in the antigen presentation process is still unclear (Kennedy, Barnes, *et al.*, 2006). Several studies have identified a large number of alleles in different loci of DLA. For instance, at DRB1, DQA1, and DQB1 loci of DLA-class II region 90, 22, and 54 alleles have been identified, respectively (Kennedy *et al.*, 2007). Also, the association of these alleles with a wide range of immune and non-immune responses has been investigated (Kennedy *et al.*, 2007; Vahedi *et al.*, 2019). The results of some of these studies are summarized below.

Canine mammary gland tumors (CMTs) are considered the most common neoplasm in female dogs. Vahedi *et al.* evaluated the DLA-DRB1 genetic polymorphism in a dog population. Subsequently, they analyzed the association of obtained MHC genotypes with mammary gland tumor profiles. According to the results, there was a significant correlation between DLA-DRB1.2 genotypes and different CMT profiles. Some genotypes were significantly associated with the increased risk of carcinoma arising in a benign tumor. Some others represented a positive correlation with complex carcinoma. Also, heterozygote genotypes were associated with a lower risk of CMT (Vahedi *et al.*, 2019). Another study evaluated the association between anal sac gland carcinoma and MHC class II loci in English Cocker Spaniels. The results revealed that the DLA-DQB1*00701 allele was associated with susceptibility to developing the carcinoma, while the allele DLA-DQB1*02001 was resistant (Aguirre-Hernández *et al.*, 2010).

Recent research in this field has not been limited to tumors. For instance, Bozorgpanah *et al.* have evaluated the association between canine atopic dermatitis and DLA-DRB1 alleles. The results showed that the presence of the type D allele in the exon II

of the DLA-DRB1 gene increases the risk of atopic dermatitis (Bozorgpanah *et al.*, 2020). In another study, Hughes *et al.* evaluated the association of a specific type of DLA class II haplotype with hypoadrenocorticism in Nova Scotia Duck Tolling Retrievers (NSDTRs). The results demonstrated that the development of hypoadrenocorticism in NSDTRs is potentially greater if the dogs are homozygous for the DLA-DRB1*01502/DQA*00601/DQB1*02301 haplotype (Hughes *et al.*, 2010). Another study on NSDTR dogs revealed an elevated risk for immune-mediated rheumatic disease (IMRD) in NSDTR dogs that were homozygous for the DLA-DRB1*00601/DQA1*005011/DQB1*02001 haplotype (Wilbe *et al.*, 2009). Moreover, Kennedy *et al.* have examined the association of canine hypothyroidism and DLA alleles in several breeds of dogs. This study indicated a significant association between the occurrence of canine hypothyroidism and the DLA class II haplotype that contains the DLADQA1*00101 allele (Kennedy, Quarmby, *et al.*, 2006). According to the results of another research, two potential DLA risk haplotypes for the canine primary immune-mediated hemolytic anemia were DLA-DRB1*00601/DQA1* 005011/DQB1*00701 and DLA-DRB1*01501/ DQA1*00601/DQB1*00301, while DLA-DRB1*00101/DQA1* 00101/DQB1*00201 was a protective one (Kennedy, Barnes, *et al.*, 2006). Several similar studies have evaluated the association between DLA haplotypes and alleles and a variety of pathological conditions in dogs, including chronic hepatitis (Bexfield *et al.*, 2012), hypoadrenocorticism (Massey *et al.*, 2013), chronic superficial keratitis (Barrientos *et al.*, 2013), pancreatic acinar atrophy (Tsai *et al.*, 2013), necrotizing meningoencephalitis (Greer *et al.*, 2010), and anal furunculosis (Barnes *et al.*, 2009).

Concluding Remarks

Due to antibiotic resistance and vaccination problems, more appropriate approaches are desired for breeding disease resistance animals, which is now practiced in cattle, sheep, chicken, and fish farming. Traditional high selection intensity for growth and production rate has caused many metabolic disorders and reduced overall immunocompetence and genetic diversity. Molecular markers associated with both resistance and fitness traits would be worthwhile in "Marker Assisted Selection" programs. The important role of MHC in disease resistance and production traits makes it a precious marker in predicting and controlling programs. It is worth noting that conserving genetic resources and diversity across populations are indispensable requirements for sustainable development. Conserving genetic resources and diversity across populations are essential requirements for sustainable development.

Acknowledgments

We would like to thank the veterinary research council of Tehran University.

Conflict of Interest

The authors declared no conflict of interest.

References

Abdurakhmonov, I. Y. (2016). Introduction to microsatellites: basics, trends and highlights. *Microsatellite Markers*. [DOI:10.5772/66446]

Abebe, A. S., Mikko, S., & Johansson, A. M. (2015). Genetic diversity of five local Swedish chicken breeds detected by microsatellite markers. *PLoS One*, *10*(4), e0120580. [DOI:10.1371/journal.pone.0120580]

Aguirre-Hernández, J., Polton, G., Kennedy, L. J., & Sargan, D. R. (2010). Association between anal sac gland carcinoma and dog leukocyte antigen-DQB1 in the English Cocker Spaniel. *Tissue Antigens*, *76*(6), 476-481. [DOI:10.1111/j.1399-0039.2010.01554.x] [PMID]

Al Naqbi, H., Mawart, A., Alshamsi, J., Al Safar, H., & Tay, G. K. (2021). Major histocompatibility complex (MHC) associations with diseases in ethnic groups of the Arabian Peninsula. *Immunogenetics*, *73*(2), 131-152. [DOI:10.1007/s00251-021-01204-x] [PMID] [PMCID]

Ali, A. O., Murphy, L., Stear, A., Fairlie-Clarke, K., Nikbakht Brujeni, G., Donskow-Łysoniewska, K., ... & Stear, M. J. (2019). Association of MHC class II haplotypes with reduced faecal nematode egg count and IgA activity in British Texel sheep. *Parasite Immunology*, *41*(7), e12626. [DOI:10.1111/pim.12626] [PMID]

Alkafajy, A., Al-Karagoly, H., & Brujeni, G. N. (2020). Comparison of cattle BoLA-DRB3 typing by PCR-RFLP, direct sequencing, and high-resolution DNA melting curve analysis. In *Veterinary Research Forum* (Vol. 11, No. 1, p. 21). Faculty of Veterinary Medicine, Urmia University, Urmia, Iran.

Alkaragoly, H., Nikbakhat Brujeni, G., Esmailnejad, A., Hasanzadeh, M., & Tolouei, T. (2018). MHC IIB Genetic Diversity and its Association With Humoral Immune Responses in Commercial Turkey. *Iranian Journal of Veterinary Medicine*, *12*(4), 347-356.

Ballingall, K. T., Fardoe, K., & McKeever, D. J. (2008). Genomic organisation and allelic diversity within coding and non-coding regions of the Ovar-DRB1 locus. *Immunogenetics*, *60*(2), 95-103. [DOI:10.1007/s00251-008-0278-2]

Barnes, A., O'Neill, T., Kennedy, L. J., Short, A. D., Catchpole, B., House, A., ... & Ollier, W. E. R. (2009). Association of canine anal furunculosis with TNFA is secondary to linkage disequilibrium with DLA-DRB1. *Tissue Antigens*, *73*(3), 218-224. [DOI:10.1111/j.1399-0039.2008.01188.x] [PMID]

Barrientos, L. S., Zapata, G., Crespi, J. A., Posik, D. M., Díaz, S., Peral-García, P., & Giovambattista, G. (2013). A study of the association between chronic superficial keratitis and polymorphisms in the upstream regulatory regions of DLA-DRB1, DLA-DQB1 and DLA-DQA1. *Veterinary Immunology and Immunopathology*, *156*(3-4), 205-210. [DOI:10.1016/j.vetimm.2013.10.009] [PMID]

Behl, J. D., Verma, N. K., Tyagi, N., Mishra, P., Behl, R., & Joshi, B. K. (2012). The major histocompatibility complex in bovines: a review. *International Scholarly Research Notices*, *2012*. [DOI:10.5402/2012/872710] [PMID] [PMCID]

Bexfield, N. H., Watson, P. J., Aguirre-Hernandez, J., Sargan, D. R., Tiley, L., Heeney, J. L., & Kennedy, L. J. (2012). DLA class II alleles and haplotypes are associated with risk for and protection from chronic hepatitis in the English Springer spaniel. [DOI:10.1371/journal.pone.0042584] [PMID] [PMCID]

Bozorgpanah, S., Jamshidi, S., Vahedi, S. M., Lankarani Mohajer, L., & Nikbakht Brujeni, G. (2020). Association of DLA-DRB1 Alleles and Canine Atopic Dermatitis. *Journal of Veterinary Research*, *75*(3), 390-398.

Briles, W. E., Bumstead, N., Ewert, D. L., Gilmour, D. G., Gogusev, J., Hala, K., ... & Wick, G. (1982). Nomenclature for chicken major histocompatibility (B) complex. *Immunogenetics*, *15*(5), 441-447. [DOI:10.1007/BF00345903]

Briles, W. E., & Briles, R. W. (1982). Identification of haplotypes of the chicken major histocompatibility complex (B). *Immunogenetics*, *15*(5), 449-459. [DOI:10.1007/BF00345904]

Nikbakht, B. G. R., Emam, M., Mahmoudzadeh, H., HAMED, M. E., Talebnia, J. R., & Rezaei, H. (2009). Typing of Ovar-DRB1 second exon with PCR-RFLP technique in Iranian Shaul Sheep.

Cinar, M. U., Mousel, M. R., Herrmann-Hoesing, L. M., Taylor, J. B., & White, S. N. (2016). Ovar-DRB1 haplotypes* 2001 and* 0301 are associated with sheep growth and ewe lifetime prolificacy. *Gene*, *595*(2), 187-192. [DOI:10.1016/j.gene.2016.10.004] [PMID]

Cruz-Tapias, P., Castiblanco, J., & Anaya, J. M. (2013). Major histocompatibility complex: antigen processing and presentation. In *Autoimmunity: From Bench to Bedside [Internet]*. El Rosario University Press.

Silva, A. P. D., & Gallardo, R. A. (2020). The chicken MHC: insights into genetic resistance, immunity, and inflammation following infectious bronchitis virus infections. *Vaccines*, *8*(4), 637. [DOI:10.3390/vaccines8040637] [PMID] [PMCID]

De, S., Singh, R. K., & Butchaiah, G. (2002). MHC-DRB exon 2 allele polymorphism in Indian river buffalo (Bubalus bubalis). *Animal Genetics*, *33*(3), 215-219. [DOI:10.1046/j.1365-2052.2002.00838.x] [PMID]

Emam, M., Mehrabani-Yeganeh, H., Barjesteh, N., Nikbakht, G., Thompson-Crispi, K., Charkhkar, S., & Mallard, B. (2014). The influence of genetic background versus commercial breeding programs on chicken immunocompetence. *Poultry Science*, *93*(1), 77-84. [DOI:10.3382/ps.2013-03475] [PMID]

Esmailnejad, A., & Brujeni, G. (2016). Study of MHC polymorphism and its linkage to IGF1 gene in Khorasan indigenous chicken. *Journal of Veterinary Research*, *71*(4).

Esmailnejad, A., Ganjiani, V., Hosseini-Nasab, E., & Nazifi, S. (2022). Association of Ovar-DRB1 alleles with innate immune responses in sheep. *Veterinary Medicine and Science*, *8*(2), 752-757. [DOI:10.1002/VMS3.683/v2/response1]

Esmailnejad, A., Brujeni, G. N., & Badavam, M. (2017). LEI0258 microsatellite variability and its association with humoral and cell mediated immune responses in broiler chickens. *Molecular Immunology*, *90*, 22-26. [DOI:10.1016/j.molimm.2017.06.027] [PMID]

Ewald, S. J., Ye, X., Avendano, S., McLeod, S., Lamont, S. J., & Dekkers, J. C. M. (2007). Associations of BF2 alleles with antibody titres and production traits in commercial pure line broiler chickens. *Animal Genetics*, *38*(2), 174-176. [DOI:10.1111/j.1365-2052.2007.01574.x]

Jamshidi, R., NIKBAKHT, B. G., Derakhshandeh, A., & Talebnia, R. (2011). Exon 2 Ovar-DRB1 gene polymorphism in the Iranian Sangsari sheep. [DOI:10.1016/j.psj.2019.11.029] [PMID] [PMCID]

Fulton, J. E. (2020). Advances in methodologies for detecting MHC-B variability in chickens. *Poultry Science*, *99*(3), 1267-1274. [DOI:10.1016/j.psj.2019.11.029] [PMID] [PMCID]

Fulton, J. E., Juul-Madsen, H. R., Ashwell, C. M., McCarron, A. M., Arthur, J. A., O'Sullivan, N. P., & Taylor, R. L. (2006). Molecular genotype identification of the Gallus gallus major histocompatibility complex. *Immunogenetics*, *58*(5), 407-421. [DOI:10.1007/s00251-006-0119-0] [PMID]

Fulton, J. E., McCarron, A. M., Lund, A. R., Pinegar, K. N., Wolc, A., Chazara, O., ... & Miller, M. M. (2016). A high-density SNP panel reveals extensive diversity, frequent recombination and multiple recombination hotspots within the chicken major histocompatibility complex B region between BG2 and CD1A1. *Genetics Selection Evolution*, *48*(1), 1-15. [DOI:10.1186/s12711-015-0181-x] [PMID] [PMCID]

Giovambattista, G., Moe, K. K., Polat, M., Borjigin, L., Hein, S. T., Moe, H. H., ... & Aida, Y. (2020). Characterization of bovine MHC DRB3 diversity in global cattle breeds, with a focus on cattle in Myanmar. *BMC Genetics*, *21*(1), 1-17. [DOI:10.1186/s12863-020-00905-8] [PMID] [PMCID]

Greer, K. A., Wong, A. K., Liu, H., Famula, T. R., Pedersen, N. C., Ruhe, A., ... & Neff, M. W. (2010). Necrotizing meningoencephalitis of Pug dogs associates with dog leukocyte antigen class II and resembles acute variant forms of multiple sclerosis. *Tissue Antigens*, *76*(2), 110-118. [DOI:10.1111/j.1399-0039.2010.01484.x] [PMID]

Han, B., Lian, L., Qu, L., Zheng, J., & Yang, N. (2013). Abundant polymorphisms at the microsatellite locus LEI0258 in indigenous chickens. *Poultry Science*, *92*(12), 3113-3119. [DOI:10.3382/ps.2013-03416]

Han, Q. H., Sun, R. N., Yang, H. Q., Wang, Z. W., Wan, Q. H., & Fang, S. G. (2019). MHC class I diversity predicts non-random mating in Chinese alligators (Alligator sinensis). *Heredity*, *122*(6), 809-818. [DOI:10.1038/s41437-018-0177-8]

Hediger, R., Ansari, H. A., & Stranzinger, G. F. (1991). Chromosome banding and gene localizations support extensive conservation of chromosome structure between cattle and sheep. *Cytogenetic and Genome Research*, *57*(2-3), 127-134. [DOI:10.1159/000133131]

Herrmann-Hoesing, L. M., White, S. N., Kappmeyer, L. S., Herndon, D. R., & Knowles, D. P. (2008). Genomic analysis of Ovis aries (Ovar) MHC class IIa loci. *Immunogenetics*, *60*(3), 167-176. [DOI:10.1007/s00251-008-0275-5]

Hughes, A. M., Jokinen, P., Bannasch, D. L., Lohi, H., & Oberbauer, A. M. (2010). Association of a dog leukocyte antigen class II haplotype with hypoadrenocorticism in Nova Scotia Duck Tolling Retrievers. *Tissue Antigens*, *75*(6), 684-690. [DOI:10.1111/j.1399-0039.2010.01440.x] [PMID]

Iglesias, G. M., Canet, Z. E., Cantaro, H., Miquel, M. C., Melo, J. E., Miller, M. M., Berres, M. E., & Fulton, J. E. (2019). Mhc-B haplotypes in "Campero-Inta" chicken synthetic line. Poultry Science. [DOI:10.3382/ps/pez431] [PMID]

Ilhan, F., Keskin, I., & Tozluca, A. (2016). Identification of genetic variation in the major histocompatibility complex gene region in Turkish sheep breeds. *South African Journal of Animal Science*, *46*(4), 366-372. [DOI:10.4314/sajas.v46i4.4]

Izadi, F., Ritland, C., & Cheng, K. M. (2011). Genetic diversity of the major histocompatibility complex region in commercial and noncommercial chicken flocks using the LEI0258 microsatellite marker. *Poultry Science*, *90*(12), 2711-2717. [DOI:10.3382/ps.2011-01721] [PMID]

Jamshidi, R., NIKBAKHT, B. G., Derakhshandeh, A., & Talebnia, R. (2011). Exon 2 Ovar-DRB1 gene polymorphism in the Iranian Sangsari sheep.

Jaworska, J., Ropka-Molik, K., Wocławek-Potocka, I., & Siemieniuch, M. (2020). Inter-and intrabreed diversity of the major histocompatibility complex (MHC) in primitive and draft horse breeds. *Plos One*, *15*(2), e0228658. [DOI:10.1371/journal.pone.0228658]

Johansson, F., & Toh, H. (2010). A comparative study of conservation and variation scores. *BMC Bioinformatics*, *11*(1), 1-11. [DOI:10.1186/1471-2105-11-388]

Keane, O. M., Dodds, K. G., Crawford, A. M., & McEwan, J. C. (2007). Transcriptional profiling of Ovis aries identifies Ovar-DQA1 allele frequency differences between nematode-resistant and susceptible selection lines. *Physiological Genomics*, *30*(3), 253-261. [DOI:10.1152/physiolgenomics.00273.2006] [PMID]

Kennedy, L. J., Barnes, A., Ollier, W. E. R., & Day, M. J. (2006). Association of a common dog leucocyte antigen class II haplotype with canine primary immune-mediated haemolytic anaemia. *Tissue Antigens*, *68*(6), 502-508. [DOI:10.1111/j.1399-0039.2006.00715.x]

Kennedy, L. J., Barnes, A., Short, A., Brown, J. J., Lester, S., Seddon, J., ... & Ollier, W. E. R. (2007). Canine DLA diversity: 1. New alleles and haplotypes. *Tissue Antigens*, *69*, 272-288. [DOI:10.1111/j.1399-0039.2006.00779.x] [PMID]

Kennedy, L. J., Quarmby, S., Happ, G. M., Barnes, A., Ramsey, I. K., Dixon, R. M., ... & Ollier, W. E. R. (2006). Association of canine hypothyroidism with a common major histocompatibility complex DLA class II allele. *Tissue antigens*, *68*(1), 82-86. [DOI:10.1111/j.1399-0039.2006.00614.x]

Konnai, S., Nagaoka, Y., Takeshima, S., Onuma, M., & Aida, Y. (2003). Sequences and diversity of 17 new Ovar-DRB1 alleles from three breeds of sheep. *European Journal of Immunogenetics*, *30*(4), 275-282. [DOI:10.1046/j.1365-2370.2003.00399.x] [PMID]

Kumari, N., Mishra, S. K., Saini, S., Kumar, A., Loat, S., Dhilor, N., ... & Kataria, R. S. (2021). Identification of novel allelic patterns and evolutionary lineage of BoLA MHC class II DQA locus in indicine and taurine cattle. *Animal Biotechnology*, 1-7. [DOI:10.1080/10495398.2021.1885426]

Li, C., Huang, R., Nie, F., Li, J., Zhu, W., Shi, X., ... & Ma, R. Z. (2020). Organization of the addax major histocompatibility complex provides insights into ruminant evolution. *Frontiers in Immunology*, *11*, 260. [DOI:10.3389/fimmu.2020.00260]

Li, H., Zhu, W., Chen, K., Song, W., Shu, J., & Han, W. (2010). Effects of the Polymorphisms of GHR Gene and IGF-1 Gene on Egg Quality in Wenchang Chicken. *Research Journal of Poultry Sciences. 3*(2), 19-22. [DOI:10.3923/rjpscience.2010.19.22]

Li, Y., Depontieu, F. R., Sidney, J., Salay, T. M., Engelhard, V. H., Hunt, D. F., ... & Mariuzza, R. A. (2010). Structural basis for the presentation of tumor-associated MHC class II-restricted phosphopeptides to CD4+ T cells. *Journal of Molecular Biology*, *399*(4), 596-603. [DOI:10.1016/j.jmb.2010.04.037]

Livant, E. J., Brigati, J. R., & Ewald, S. J. (2004). Diversity and locus specificity of chicken MHC B class I sequences. *Animal Genetics*, *35*(1), 18-27. [DOI:10.1111/j.1365-2052.2003.01078.x] [PMID]

Lwelamira, J., Kifaro, G. C., & Gwakisa, P. S. (2009). Genetic parameters for body weights, egg traits and antibody response against Newcastle Disease Virus (NDV) vaccine among two Tanzania chicken ecotypes. *Tropical Animal Health and Production*, *41*(1), 51-59. [DOI:10.1007/s11250-008-9153-2] [PMID]

Manjula, P., Fulton, J. E., Seo, D., & Lee, J. H. (2020). Major histocompatibility complex B variability in Korean native chicken breeds. *Poultry Science*, *99*(10), 4704-4713. [DOI:10.1016/j.psj.2020.05.049] [PMID] [PMCID]

Manjula, P., Kim, M., Cho, S., Seo, D., & Lee, J. H. (2021). High levels of genetic variation in MHC-linked microsatellite markers from native chicken breeds. *Genes*, *12*(2), 240. [DOI:10.3390/genes12020240]

Manlik, O., Krützen, M., Kopps, A. M., Mann, J., Bejder, L., Allen, S. J., ... & Sherwin, W. B. (2019). Is MHC diversity a better marker for conservation than neutral genetic diversity? A case study of two contrasting dolphin populations. *Ecology and Evolution*, *9*(12), 6986-6998. [DOI:10.1002/ece3.5265] [PMID] [PMCID]

Martin, A., Dunnington, E. A., Gross, W. B., Briles, W. E., Briles, R. W., & Siegel, P. B. (1990). Production traits and alloantigen systems in lines of chickens selected for high or low antibody responses to sheep erythrocytes. *Poultry Science*, *69*(6), 871-878. [DOI:10.3382/ps.0690871] [PMID]

Massey, J., Boag, A., Short, A. D., Scholey, R. A., Henthorn, P. S., Littman, M. P., ... & Kennedy, L. J. (2013). MHC class II association study in eight breeds of dog with hypoadrenocorticism. *Immunogenetics*,

65(4), 291-297. [DOI:10.1007/s00251-013-0680-2] [PMID]

Matzaraki, V., Kumar, V., Wijmenga, C., & Zhernakova, A. (2017). The MHC locus and genetic susceptibility to autoimmune and infectious diseases. *Genome Biology*, *18*(1), 1-21. [DOI:10.1186/s13059-017-1207-1] [PMID] [PMCID]

McMahon, R. M., Friis, L., Siebold, C., Friese, M. A., Fugger, L., & Jones, E. Y. (2011). Structure of HLA-A* 0301 in complex with a peptide of proteolipid protein: insights into the role of HLA-A alleles in susceptibility to multiple sclerosis. *Acta Crystallographica Section D: Biological Crystallography*, *67*(5), 447-454. [PMCID] [DOI:10.1107/S0907444911007888] [PMID]

Medina, N. P., De Guia, A. C. M., Venturina, V. M., & Mingala, C. N. (2019). Molecular characterization of MHC II DRB3 gene of swamp- and riverine-type water buffaloes. *Journal of Advanced Veterinary and Animal Research, 6*(3), 308-314. [DOI:10.5455/javar.2019.f349] [PMID] [PMCID]

Miller, M. M., & Taylor Jr, R. L. (2016). Brief review of the chicken major histocompatibility complex: the genes, their distribution on chromosome 16, and their contributions to disease resistance. *Poultry Science*, *95*(2), 375-392. [DOI:10.3382/ps/pev379] [PMCID]

Mpenda, F. N., Tiambo, C. K., Juma, J., Pelle, R., Lyantagaye, S. L., & Buza, J. (2020). Association of LEI0258 marker alleles and susceptibility to virulent newcastle disease virus infection in kuroiler, sasso, and local Tanzanian Chicken Embryos. *Journal of Pathogens*, *2020*. [DOI:10.1155/2020/5187578] [PMID] [PMCID]

Mwambene, P. L., Kyallo, M., Machuka, E., Githae, D., & Pelle, R. (2019). Genetic diversity of 10 indigenous chicken ecotypes from Southern Highlands of Tanzania based on Major Histocompatibility Complex-linked microsatellite LEI0258 marker typing. *Poultry Science*, *98*(7), 2734-2746. [DOI:10.3382/ps/pez076] [PMID] [PMCID]

Nakamura, T., Shirouzu, T., Nakata, K., Yoshimura, N., & Ushigome, H. (2019). The role of major histocompatibility complex in organ transplantation-donor specific anti-major histocompatibility complex antibodies analysis goes to the next stage. *International Journal of Molecular Sciences*, *20*(18), 4544. [DOI:10.3390/ijms20184544] [PMCID]

Nikbakht Brujeni, G., Ghorbanpour, R., & Esmailnejad, A. (2016). Association of BoLA-DRB3. 2 alleles with BLV infection profiles (persistent lymphocytosis/lymphosarcoma) and lymphocyte subsets in Iranian Holstein cattle. *Biochemical Genetics*, *54*(2), 194-207. [DOI:10.1007/s10528-016-9712-6] [PMID]

Nikbakhat, G., Tajbakhsh, H., Mokhber Dezfooli, M., Zahrai Salehi, T., Rabani, M., Gharibi, D., ... & Khormali, M. (2011). Association between amino acid sequences in peptide binding region (BOLA-DRB3) and susceptibility or resistance to calf diarrhea. *Journal of Veterinary Research*, *66*(1), 23-52.

Nikbakht, G., & Esmailnejad, A. (2015). Chicken major histocompatibility complex polymorphism and its association with production traits. *Immunogenetics*, *67*(4), 247-252. [DOI:10.1007/s00251-015-0832-7] [PMID]

Nikbakht, G., Esmailnejad, A., & Barjesteh, N. (2013). LEI0258 microsatellite variability in Khorasan, Marandi, and Arian chickens. *Biochemical Genetics*, *51*(5), 341-349. [DOI:10.1007/s10528-013-9567-z] [PMID]

Nikbakht, G., Rezaii, H., Stear, M. J., Talebi, M. A., & Mahmoudzadeh, H. (2012). Allelic polymorphism in the second exon of Ovar-DRB1 in fat-tailed sheep. *The Veterinary Journal*, *192*(3), 547-549. [DOI:10.1016/j.tvjl.2011.08.025] [PMID]

Niskanen, A. K., Kennedy, L. J., Lohi, H., Aspi, J., & Pyhäjärvi, T. (2016). No evidence of prenatal diversifying selection at locus or supertype levels in the dog MHC class II loci. *Canine Genetics and Epidemiology*, *3*(1), 1-12. [DOI:10.1186/s40575-016-0038-9] [PMID] [PMCID]

Othman, O. E., Khodary, M. G., El-Deeb, A. H., & Hussein, H. A. (2018). Five BoLA-DRB3 genotypes detected in Egyptian buffalo infected with Foot and Mouth disease virus serotype O. *Journal of Genetic Engineering and Biotechnology*, *16*(2), 513-518. [DOI:10.1016/j.jgeb.2018.02.009] [PMID] [PMCID]

Radwan, J., Babik, W., Kaufman, J., Lenz, T. L., & Winternitz, J. (2020). Advances in the evolutionary understanding of MHC polymorphism. *Trends in Genetics*, *36*(4), 298-311. [DOI:10.1016/j.tig.2020.01.008] [PMID]

Ranjbar, M. M., Ataei, S., Nikbakht Brujeni, G., & Golabdar, S. (2017). Analysis of variations, structures, and phylogenic characteristics of bovine leukocyte antigen DRB3 exon2. *Archives of Razi Institute*, *72*(3), 147-157.

Ranjbar, M. M., Nikbakht, G., Ghadrdan Mashhadi, A. R., & Dabbaghyan, M. (2016). Study of BuLA-DRB3 polymorphism in Khuzestan river buffaloes. Journal of Veterinary Research.

Rock, K. L., Reits, E., & Neefjes, J. (2016). Present yourself! By MHC class I and MHC class II molecules. *Trends in Immunology*, *37*(11), 724-737. [DOI:10.1016/j.it.2016.08.010] [PMID] [PMCID]

Sayers, G., Good, B., Hanrahan, J. P., Ryan, M., Angles, J. M., & Sweeney, T. (2005). Major histocompatibility complex DRB1 gene: its role in nematode resistance in Suffolk and Texel sheep breeds. *Parasitology*, *131*(3), 403-409. [DOI:10.1017/S0031182005007778] [PMID]

Scott, P. C., Maddox, J. F., Gogolin-Ewens, K. J., & Brandon, M. R. (1992). The nucleotide sequence and evolution of ovine MHC class II B genes: DQB and DRB. *Immunogenetics*, *35*(3), 217-217. [DOI:10.1007/BF00185117] [PMID]

Sehnal, D., Bittrich, S., Deshpande, M., Svobodová, R., Berka, K., Bazgier, V., ... & Rose, A. S. (2021). Mol* Viewer: modern web app for 3D visualization and analysis of large biomolecular structures. *Nucleic Acids Research*, *49*(W1), W431-W437. [DOI:10.1093/nar/gkab314] [PMID] [PMCID]

Shen, H., Han, G., Jia, B., Jiang, S., & Du, Y. (2014). MHC-DRB1/DQB1 gene polymorphism and its association with resistance/susceptibility to cystic Echinococcosis in Chinese Merino sheep. *Journal of Parasitology Research*, *2014*. [DOI:10.1155/2014/272601] [PMID] [PMCID]

Siva Subramaniam, N., Morgan, E. F., Wetherall, J. D., Stear, M. J., & Groth, D. M. (2015). A comprehensive mapping of the structure and gene organisation in the sheep MHC class I region. *BMC Genomics*, *16*(1), 1-17. [DOI:10.1186/s12864-015-1992-4] [PMID] [PMCID]

Tizard, I. R. (2018). Immune-mediated inflammatory disease. *Veterinary Immunology. 10th ed.. St. Louis, Missouri, USA: Elsevier*, 423-434.

Tsai, K. L., Starr-Moss, A. N., Venkataraman, G. M., Robinson, C., Kennedy, L. J., Steiner, J. M., & Clark, L. A. (2013). Alleles of the major histocompatibility complex play a role in the pathogenesis of pancreatic acinar atrophy in dogs. *Immunogenetics*, *65*(7), 501-509. [DOI:10.1007/s00251-013-0704-y]

Tumer, G., Simpson, B., & Roberts, T. K. (2019). Genetics, human major histocompatibility complex (MHC).

Vahedi, S. M., Nikbakht, G., Jamshidi, S., Lankarani, L., Alimi, N., & Esmailnejad, A. (2019). Association between DLA-DRB1. 2 allelic diversity and development of mammary gland tumors in dogs. *Acta Veterinaria Scandinavica*, *61*(1), 1-8. [DOI:10.1186/s13028-019-0491-z. PMID: 31727096.] [PMID] [PMCID]

Vieira, M. L. C., Santini, L., Diniz, A. L., & Munhoz, C. D. F. (2016). Microsatellite markers: what they mean and why they are so useful. *Genetics and Molecular Biology*, *39*, 312-328. [DOI:10.1590/1678-4685-GMB-2016-0027] [PMID] [PMCID]

Wagner, J. L. (2003). Molecular organization of the canine major histocompatibility complex. *Journal of Heredity*, *94*(1), 23-26. [DOI:10.1093/jhered/esg002] [PMID]

White, S. N., & Knowles, D. P. (2013). Expanding possibilities for intervention against small ruminant lentiviruses through genetic marker-assisted selective breeding. *Viruses*, *5*(6), 1466-1499. [DOI:10.3390/v5061466] [PMID] [PMCID]

Wieczorek, M., Abualrous, E. T., Sticht, J., Álvaro-Benito, M., Stolzenberg, S., Noé, F., & Freund, C. (2017). Major histocompatibility complex (MHC) class I and MHC class II proteins: conformational plasticity in antigen presentation. *Frontiers in Immunology*, *8*, 292. [DOI:10.3389/fimmu.2017.00292] [PMID] [PMCID]

Wilbe, M., Jokinen, P., Hermanrud, C., Kennedy, L. J., Strandberg, E., Hansson-Hamlin, H., ... & Andersson, G. (2009). MHC class II polymorphism is associated with a canine SLE-related disease complex. *Immunogenetics*, *61*(8), 557-564. [DOI:10.1007/s00251-009-0387-6] [PMID]

Wosen, J. E., Mukhopadhyay, D., Macaubas, C., & Mellins, E. D. (2018). Epithelial MHC class II expression and its role in antigen presentation in the gastrointestinal and respiratory tracts. *Frontiers in Immunology*, 2144. [DOI:10.3389/fimmu.2018.02144] [PMID] [PMCID]

Wu, T. T., & Kabat, E. A. (1970). An analysis of the sequences of the variable regions of Bence Jones proteins and myeloma light chains and their implications for antibody complementarity. *The Journal of Experimental Medicine*, *132*(2), 211-250.

Yuan, Y., Zhang, H., Yi, G., You, Z., Zhao, C., Yuan, H., ... & Lian, L. (2021). Genetic Diversity of MHC BF/BL Region in 21 Chicken Populations. *Frontiers in Genetics*, *12*. [DOI:10.3389/fgene.2021.710770]

Zakharova, M. Y., Belyanina, T. A., Sokolov, A. V., Kiselev, I. S., & Mamedov, A. E. (2019). The contribution of major histocompatibility complex class II genes to an association with autoimmune diseases. *Acta Naturae, 11*(4), 4-12. [DOI:10.32607/20758251-2019-11-4-4-12] [PMID] [PMCID].

10.22059/IJVM.2022.339598.1005251

Iranian Journal of Veterinary Medicine

Abstracts in Persian Language

Online ISSN 2252-0554

مجله طب دامی ایران، ۱۴۰۱، دوره ۱۶، شماره ۳، ۲۱۱-۲۲۷

مجتمع عمده پذیرش بافتی به عنوان شاخص انتخاب برای پرورش حیوان ایمن

غلامرضا نیکبخت بروجنی*[۱]، پویا هوشمند[۱]، عاطفه اسماعیل نژاد[۲] ، فاطمه عباس‌آبادی[۱]

[۱]. *گروه میکروبیولوژی و ایمونولوژی، دانشکده دامپزشکی دانشگاه تهران، تهران، ایران*

[۲]. *گروه پاتوبیولوژی، دانشکده دامپزشکی دانشگاه شیراز، شیراز، ایران*

(دریافت مقاله: ۱۸ اسفند ماه ۱۴۰۰، پذیرش نهایی: ۲۰ اردیبهشت ۱۴۰۱)

با توجه به تهدیدات ناشی از مشکلات واکسیناسیون و مقاومت آنتی بیوتیکی، طرح روش‌های جدید برای پرورش حیوانات مقاوم ضروری به نظر می‌رسد. این روش‌ها هم‌اکنون نیز در حوزه پرورش دام‌های بزرگ، پرندگان و ماهی‌ها به کار برده می‌شوند. در طول سدهٔ گذشته، سازوکارهای پرورش حیوانات، که عمدتا بر اساس ویژگی‌های ظاهری و فنوتیپی بوده، سبب افزایش نرخ رشد و تولید و بهره اقتصادی بیشتر شده است. با وجود مزایای این سازوکار، پرورش حیوانات تنها با توجه به ویژگی‌های ظاهری می‌تواند منجر به بروز طیف وسیعی از ناهنجاری‌های فیزیولوژیک و کاهش توانایی عملکرد سیستم ایمنی در نتاج شود. این موضوع لزوم توجه به عوامل ژنتیکی دخیل در پرورش حیوانات را یادآور می‌شود. یکی از مهم‌ترین خوشه‌های ژنی شناسایی شده در حیوانات، مجتمع عمده پذیرش بافتی (MHC) است. این مجموعه ژن نقشی حیاتی در عملکرد مطلوب سیستم ایمنی و شناسایی مولکول‌های خودی از غیرخودی ایفا می‌کند. مطالعات اخیر نشان داده‌اند که برخی از مناطق موجود در خوشه ژنی MHC دارای تنوع آللی گسترده‌ای هستند. همچنین، ارتباط معناداری بین آلل‌های مختلف MHC و حساسیت/مقاومت به انواعی از بیماری‌های عفونی شناخته شده است. این مقاله مروری است بر پژوهش‌های انجام شده در حوزه شناسایی تنوع آللی MHC و ارتباط آن‌ها با پاسخ‌های ایمنی در حیوانات اهلی.

واژه‌های کلیدی: پاسخ ایمنی، تنوع آللی، حیوان ایمن، شاخص انتخاب، مجتمع عمده پذیرش بافتی

نویسندهٔ مسئول: دکتر غلامرضا نیکبخت بروجنی، گروه میکروبیولوژی، دانشکده دامپزشکی دانشگاه تهران، تهران، ایران ایمیل nikbakht@ut.ac.ir