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BOLA Gene Polymorphism and Determination of Disease Severity and Susceptibility: Review

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Abstract: Major histocompatibility complex is the gene complex that exists in all vertebrae like humans (HLA), dogs (DLA), bovine (BLA), ovine (OLA), swine (SLA), and equine (ELA). MHC possesses three regions (I, II, III) that control major specific immune responses and contain variety of genes which influence growth, development, reproduction, odor, and olfaction. Measuring levels of polymorphism of these genes can provide indirect measures of the immunological fitness of populations. As humans and mice, cattle have three MHC gene classes (class I, II, and III). Both BoLA class I and II play a role in antigen presentation, however the function of BoLA class III has been releated with components of the complement system. BoLA class II region is extra separated into class IIa and class IIb. In this gene, the genetic polymorphism of class II α and β genes occurs predominantly in exon 2 encoding the antigen binding site. The BoLa-A locus has 32 serologically defined alleles and minimum four further putative alleles in addition to a high frequency of null alleles. With association allele hold DRB3.2*8 (DRB3*1201) and DRB3.2*16 (DRB3*1501) genes are associated with mastitis susceptibility, and DRB3.2*22 (DRB3*1101), DRB3.2*23 (DRB3*2703) and DRB3.2*24 (DRB3*0101) with mastitis resistance. The A8 specificity and the EIAY sequence are significant markers of resistance, while the serine residue is a marker of susceptibility to dermatophlosis. According to the report 2004, BoLA-DRB3 alleles with the amino acid residues Glu, Arg, and valine (Val) at positions 74, 77, and 78, respectively, give resistance to tumor development by BLV infection. On the other hand, HaeIII CC and HaeIII BC genotypes were actually associated with resistance to FMD in contrast, the HaeIII AA genotype was associated with susceptibility to FMD. Another report on infected Egyptian buffaloes with serotype O FMDV genotype AA for FMD resistance while genotype AC for susceptibility to FMD.

Keywords: Major Histocompatibility Complex, Bovine lymphocyte Antigen, Polymorphism, Susceptibility and Resistivity

1. Introduction

Major histocompatibility complex (MHC) is the term used to describe a genetic complex found in virtually all vertebrates. MHC varies with the species, such that in humans the MHC is termed HLA (Human lymphocyte antigen) and in the mouse, it is called H-2, in swine SLA (Swine lymphocyte Antigen), in ovine OLA (Ovine lymphocyte Antigen), in equine ELA (Equine lymphocyte Antigen), in dogs DLA (Dog lymphocyte Antigen) and bovine BoLA (Bovine lymphocyte Antigen [24]. Major histocompatibility genes was discovered by means of tissue and organ transplantation from donors that differed genetically from the recipients and have been genetically implicated in several human autoimmune diseases [10].

The MHC region possesses two different class I and II genes that control all specific immune responses. But it had many other genes that act on growth, development, reproduction, odor, and olfaction [22]. Class I MHC genes encode particular glycoproteins on every nucleated cell of the body and a major played by this class of molecule is the presentation of peptide antigens to Tc (cytotoxic T-cells), while Class II MHC genes encode for the glycoproteins, which are expressed only on the surface of antigen-presenting cells (APCs) like macrophages, dendritic cells, and B-cells [29]. MHC genes play key roles in immune responses to infectious diseases and self/non-self-recognition. Matching MHC alleles is also critical for organ transplantation, and changes in the MHC profile of tumor cells allow effective evasion of the immune response [43].

The delegation of the MHC molecules based on the polymorphism of the T-lymphocyte receptors which in turn determine the disease and parasite resistance of an organism and thus may influence the long-term survival probability of populations [32]. Consequently, estimating stages of polymorphism in these genes forward indirect measures of the immunological fitness of populations [36]. This polymorphism is characterized by two features a large number of alleles at a given functional locus and a large number of nucleotide differences between some of the alleles. Recent data indicate that the polymorphic differences accumulate over periods much longer than the life span of a species and that they are passed on from ancestral to emerging species during speciation [18].

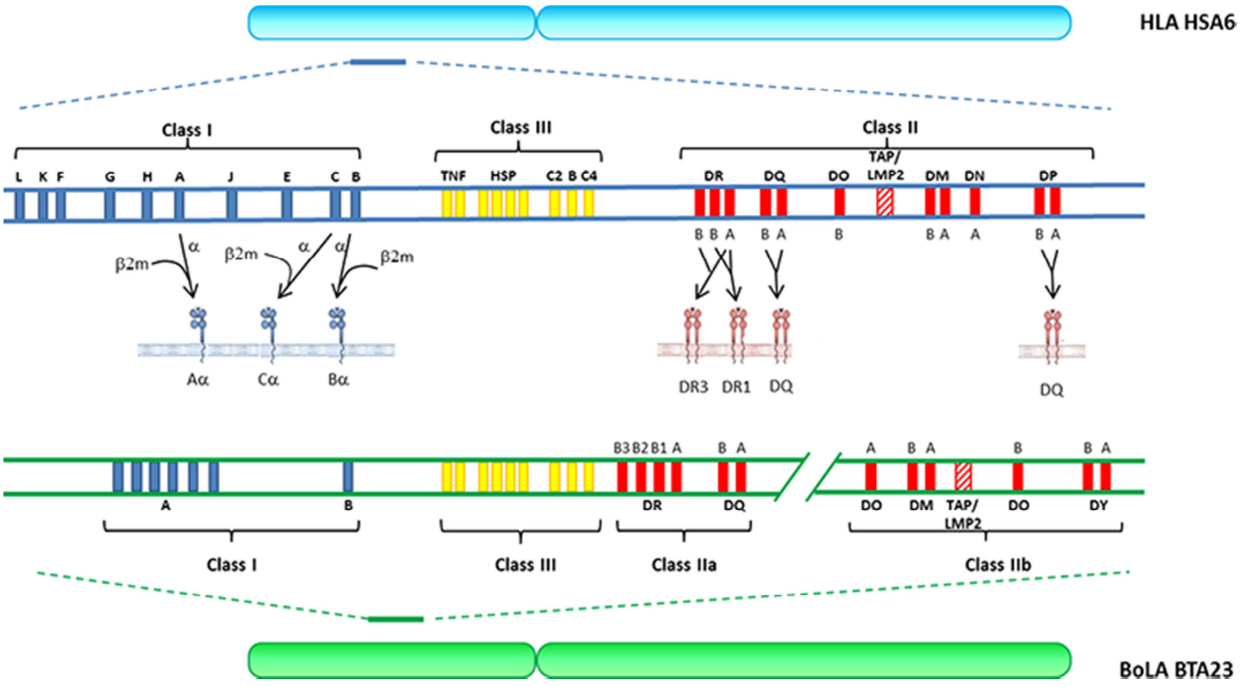
The arrangement of this gene structurally and organization in cattle is known as the bovine leukocyte antigen (BoLA) complex [2]. Bovine leukocyte antigens are used extensively as markers of disease and immunological traits in cattle [30]. MHC classII has two distinctive gene coding sub-region (DQ, DR), cattle express one DR gene pair (DRA and DRB3) and one or two DQ gene pairs per haplotype [15, 25, 35]. As reported by different authors BoLA-DR3 range has strong correlations with different bovine infectious disease susceptibility and resistivity like bovine leukemia virus, dermatophilosis, and mastitis [14, 26, 39]. Additionally, BoLA-DRB3 played a key role in the immune response to foot-and-mouth disease [11, 12]. Both Wei [38] and Lei [12] confirm that BoLA DR3 polymorphism possesses different alleles purposively used for FMD resistivity and susceptibility in bovines.

2. BoLA Gene Polymorphism

Major Histocompatibility Complex (MHC) or BoLA (Bovine Lymphocyte Antigen) is polymorphic gene found on lymphocyte surface nucleated antigen of ovine cell, which has high immunogenic capacity than other surface antigens [9]. The bovine lymphocyte antigen (BoLA-DRB3) gene encodes cell surface glycol-proteins that initiate immune responses by presenting processed antigenic peptides to CD4 T helper cells [15].

As humans and mice, cattle have three MHC gene classes (class I, II, and III). Class I and II both highly participating on antigen presentation, while the function of BoLA class III has been associated with components of the complement system. BoLA class II region is further divided into class IIa and class IIb [21]. The BoLA gene is located on the short arm of bovine chromosome 23. Genotyping of BoLA is comparatively complex due to the genes within this family are very polymorphic. The genetic polymorphism of class II α and β genes occurs predominantly in exon 2 encoding the antigen binding site. With recently report above 100 diverse alleles from exon 2 of the BoLA-DRB3 gene have been recognized [5].

Total size of class I region ranges from 770 Kb to 1650 Kb. There are two tightly linked expressed loci (BoLA- A and BoLA-B) in the BoLA class I regions that are within 200 Kb of each other. The genomic organization of the MHCs of ruminants differs from that of mice and humans as class II region in ruminants is split into two sub-regions which are separated by at least 15cM (from DYA in the class IIb region to DRB3 in class IIa region) [6]. Molecular analysis of the MHC class I region suggested that this region may contain up to 15 genes. The BoLa-A locus has 32 serologically defined alleles at least four more putative alleles and, a high frequency of null alleles [7, 20].



Source: [23]

Figure 1. *Bovine lymphocyte antigen (BoLA).*

BoLA class II region has numerous unusual morphology, including separation of the DR and DQ genes from the LMP2, DOA and DOB genes by a large recombination distance. The region containing the LMP2, DOA and DOB genes also includes the DYA and DIB genes [3]. The class IIa sub-region contains the functionally expressed DR and DQ genes and among the three DRB genes, DRB3 is believed to be functionally important. The DRB3 gene is the most polymorphic class II locus in cattle and influences both the magnitude and epitope specificity of antigen-specific T cell responses to infectious diseases [23] (figure 1).

3. BOLA DR3 in Determining Disease Resistivity and Susceptibility

3.1. BoLA-DRB3 Gene Polymorphism to Mastitis

Mastitis disease was caused by pathogenic bacteria like Streptococci, coagulase-negative Staphylococci (CNS), Escherichia coli, Staphylococcus aureus, or other pathogens [40]. The SCC (somatic cell count) in milk was the most indicative index of mastitis in diagnosis of the relationship between BoLA-DRB3 alleles and mastitis [26, 27, 28, 33]. Cows with a SCC of < 200 000 cells/mL are not likely to be affected with major mastitis pathogens while caws SCC> 300 000 are infected with mastitis pathogen bacteria [16]. Those cells can recognize foreign antigens and initiate phagocytosis is controlled by the immune response mediated by the major histocompatibility antigen complex or BOLA in bovine [40]. But, there is great disagreement on association of SCC and BOLA DR3 on resistivity and susceptibility of mastitis.

According to Rupp, 1997 report DRB3.2*16 was associated with a high SCC, whereas DRB3.2*22 was associated with a low SCC; furthermore, DRB3.2*11, DRB3.2*12 and DRB3.2*23 were associated with high mastitis resistance [42]. This contradicted by achievement DRB3.2*23 was associated with high mastitis susceptibility and DRB3.2*16 with a low SCC [28]. But report in 2012 state that DRB3.2*8 (DRB3*1201) and DRB3.2*16 (DRB3*1501) are associated with mastitis susceptibility, and DRB3.2*22 (DRB3*1101), DRB3.2*23 (DRB3*2703) and DRB3.2*24 (DRB3*0101) with mastitis resistance [40]. This contradict was risen from sample size problem, lack of long term SCC pried, absence of full history of animal like any medication during milk collection and mult-factoral nature of the immune response to various pathogens that cause mastitis.

3.2. BoLA-DRB3 Gene Polymorphism to Dermatophlosis

Dermatophilosis is the disease affect which caused by infection with the Actynomycete *Dermatophilus congolensis* [37]. The thick prevalence was specific point that out ward the severity of infection, and the tick saliva was the most important for immunosuppressive agent favoring the disease. As control strategy using antibiotic for affected animal and controlling of tick are the major [14]. According to Maillard in 1996 show that there is best correlation with these BoLA class I and class II markers and the characters of resistance or susceptibility to dermatophilosis [14].

The A8 specificity and the EIAY sequence are significant markers of resistance, whereas the serine residue is a marker of susceptibility. The best relationship with resistance character (p value <0.001) was gained by the correlation in a sume animal, of the class I A8 specificity, the class I1 EIAY sequence, and the lack of the amino acid serine in ARS position 30 [14].

3.3. BoLA-DRB3 Gene Polymorphism to Bovine Leukemia Virus

The correlation between the amino acid motifs in *BoLA-DRB3* alleles and Bovine leukemia virus resistance or susceptibility in cattle indicate that *BoLA-DRB3* alleles with glutamic acid (Glu) and arginine (Arg) residues at positions 70 and 71 of pocket 4 were associated with resistance to persistent lymphocytosis caused by bovine leukemia virus (BLV) [39]. According to Aida, 2004 [1], *BoLA-DRB3* alleles with the amino acid residues Glu, Arg, and valine (Val) at positions 74, 77 and 78, respectively, give resistance to tumor development by BLV infection [28] Chieh-Wen also report his achievement among comparison of BoLA, BLV and PVL (proviral load) the BoLA-DRB3 polymorphism confers differential susceptibility to BLV-induced lymphoma and PVL [13].

3.4. BoLA-DRB3 Gene Polymorphism to FMD

Baxtera *et al.* report that in 2009 DRB3 alleles best gene to indicate the level immune response after he report the correlation between bovine MHC DRB3 alleles and their binding pockets with the immune response to a 40-mer peptide derived from FMDV VP1 [4]. This association necessary for immune response due to the exist to T cells, is dependent on the interactions between peptide side chains and pockets within the peptide binding cleft [31, 34]. A reported by Wei, 2012 [38] and Lei, (2012) HaeIII CC and HaeIII BC genotype were related with resistance to FMD in contrast, HaeIII AA genotype was related with susceptibility to FMD [12, 38]. Another report on infected Egyptian buffaloes with serotype O FMDV genotype AA for FMD-resistance while genotype AC for susceptibility to FMD HaeIII AA [19]. The finding in 2022 on Susceptibility to FMD virus infection in vaccinated cattle, and host BoLA A and BoLA DRB3 genes polymorphism similarly provide the polymorphism effect on disease susceptibility as disorder in the amino acid residues of BoLA A gene might also possess some acts in determining susceptibility of vaccinated animals to foot and mouth disease virus infection [8, 17].

4. Conclusion

The Major histocompatibility complex or Bovine lymphocyte antigen in bovine was gene which was high

polymorphic, that mark it crucial in different genetically activity of animal production and correlation between animal and microorganism. BoLA was surface antigen located more over on lymphocyte which is immunogenic. This immunogenicity was accomplished by initiation of immune response by presenting processed antigen peptide to CD4 T-helper cell to coordinate the immune response by stimulating other immune cells. Existence of this Allele hold this gene was better to protection of animal from disease if not exposed to disease susceptibility. Based on this short concise information it's better to investigated intensely on Bovine lymphocyte antigen to decrease or control the effect of pathogenic microorganism on animal life and production.

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