RESEARCH ARTICLE

Bovine Disease-Related DNA Mutations and Their Genetic Control Strategies in Breeding for Disease Resistance

Edward Nehemiah, Armand Kennan
Department of Clinical Researches, School of Genetic Medicine, India

Abstract: Bovine genomic DNA mutations and their genetic effects on gene expression and protein function influence disease susceptibility and resistance of cattle. The genetic loci related to cattle diseases are mainly divided into two types: single-locus-disease genes and multigenic-disease loci. The single-locus-disease genes are called causal mutations; their genetic basis is simply and normally detected in the coding and non-coding regions inducing substitution of amino acid, premature termination of translation, and complete deletion of entire exon(s). In contrast, the genetic basis of disease related to multiple genes is more complex since susceptibility or resistance of these diseases is affected by the interactions among host, pathogen, and environment. This article reviewed current research and application of the major diseases of cattle con- trolled by single gene or polygenic genes. The genetic control strategies of effective identification and control of these dis- eases in bovine breeding and production were also analyzed.

Keywords: Cattle; casual mutation; genetic disease; complex disease; genetic control; methods

With the clarification of genetic material and the rapid development of molecular genetic technology, a great deal of genetic variation information related to human diseases has been excavated in the past 50 years. Livestock genomes, like humans, contain a wealth of genetic variations, usually manifested as single nucleotide polymorphisms (SNPs), deletion or inser tion of nucleotide fragments (Nucleotide deletion/inser-tion), chromatin rearrangement, and gene duplication. Copy number polymorphisms (including variable tandem repeats and microsatellites), copy number variation (CNV), insertion or deletion of DNA fragments 1 KB or longer), and transposon insertion/presence/deletion

Absence, such as Alu component)[1,2]. It was found that these DNA variations, though accounting for only about 1% of the entire genome, constitute the genetic basis for individual variations and disease resistance or susceptibility in livestock and poultry[3]. DNA mutations located in gene coding and regulatory regions have the ability to modify gene expression and affect protein function, and have beneficial or harmful effects on animal productivity and health.

At present, cattle genome sequencing sketch has been completed, these genome polymorphism information for its production performance, longevity, adaptability and disease resistance research provides information. A great deal of achievements have been made in the study of genes related to cattle production performance, but there are not many genes related to disease resistance[4].

The research and application of genetic basis of bovine diseases mainly include two aspects: first, discovering and identifying genes or markers related to disease or disease resistance; second, using the genetic basis of disease for disease resistance breeding, thus providing products beneficial to human health. In the past 20 years, single-locus-controlled genetic diseases, such as cow vertebral malformation (CVM), have been eliminated by eliminating individuals or carriers with pathogenic genes. However, the genetic basis of some common infectious diseases, such as mastitis and brucellosis, is complex. The interaction between organism, pathogen and environment plays an important

doi: 10.18063/gds.v2i1.

role. It is an important direction to elucidate the resistance mechanism of these complex diseases in the future. In this paper, we summarized and analyzed the related genes and mutation types of main diseases in cattle, and discussed how to control the occurrence of cattle diseases effectively according to DNA mutation information and disease-resistant individual selection in cattle breeding and production.

1. Single locus mutation leading to bovine diseases

According to statistics, more than 100 cattle diseases are caused by single-locus-disease gene mutations, also known as Causal mutations (Fig. 1). Diseases caused by causal mutations are often referred to as genetic defects. Causal mutations in cattle diseases are currently less than one-twentieth clear (Table 1). It was found that these mutations mainly existed in the coding or non-coding regions of genes and caused diseases by affecting the modification of mRNA and protein stability (http://www.ncbi.nlm.nih.gov/omia, NCBI OMIA: Online Mendelian In-heritance in Animals)[4]. The major diseases of cattle caused by these two major single locus mutations are summarized below.

1.1 Causal mutation in coding region

The most common type of amino acid mutation is the single base mutation[7], dairy cow vertebral malformation syndrome (CVM) is such a genetic disease (Table 1). Thomsen *et al*. found that the mutant base was located at site 559 of the SLC35A3 gene, where guanine was in the chest Substitution of adenine pyrimidine (G559T) resulted in the 180th position of valine to phenylalanine (V180F). Abnormal nucleoside-glucose complex is produced when the mutation is homozygous. When the abnormal complex is transported to Golgi, the normal process of protein glycosylation will be disrupted, resulting in abortion, stillbirth or malformation of pregnant dairy cows. Another important cause-and-effect mutation in Holstein cattle is located in the highly conserved region (A383G) of the CD18 gene. This mutation results in amino acid changes (Asp128Gly) in the extracellular glycoprotein. This mutation has a decisive effect on Leukocyte adhesion deficiency (LAD) in Holstein cattle[9]. CVM and LAD are the most common genetic diseases in Holstein cattle, which are detected in most Holstein cattle herds worldwide[10–12].

The second type is the mutation of codons encoding amino acids into termination codons or nonsense codons that terminate translation or produce dysfunctional proteins in advance, leading to different genetic diseases. Bovine myoclonus is caused by a C156A mutation in the GLRA1 gene that causes the tyrosine codon in exon 2 to become the termination codon[13]. The termination codon led to premature termination of protein synthesis, resulting in protein deficiency. Bovine beta-mannosidase storage disorder is caused by a nonsense mutation in the MANBA gene (G2574A) resulting in the loss of 22 amino acids at the C-terminal of the protein, suggesting that the base of this locus plays an important role in the stability and function of beta-mannosidase[14]. Bovine uridine synthase deficiency is also due to a C405T mutation in the UMPS gene, which transforms the arginine codon (CGA) into the termination codon (TGA), resulting in the loss of 76 amino acids at the C terminal of the enzyme[15].

The third is that different SNPs within the same gene leads to the same genetic diseases of different varieties. Bovine lysosomal alpha mannose glycoside disease was found in different cattle breeds. In Angus cattle, the disease was caused by a T to C mutation at position 961 of the MAN2B1 gene, which resulted in the change of codon 321 from phenylalanine to leucine. However, in Galloway cattle, the disease is due to G to A mutation at position 662 of MAN2B1 gene, resulting in the 221 arginine codon to histidine[16]. The substituted phenylalanine and arginine play an important role in the protein function of the alpha-mannosidase family. When they are substituted by other amino acids, they can not play a normal protein function, resulting in the defect of lysosomal alpha-mannosidase. Bovine Maple diabetes mellitus (MSUD)[17,18] and glycogen accumulation type II[19] are also caused by this type of gene mutation.

Another is the deletion or insertion of a single base, a base fragment, or an entire gene in the exon region of a gene. Such mutations cause frame-shifting mutations that have a greater impact on protein function and thus cause genetic diseases. Bovine VII type AI syndrome is due to a 17 bp deletion of ADAMTS2 gene[20]. In addition, abnormal development of bovine renal tubular[21–23] is also caused by deletion of base fragments. In addition, bovine diaphragmatic myopathy [24] and bovine XY female inversion syndrome[25] were caused by complete loss of protein activity due to the deletion of the whole gene.

1.2 Causal mutations in non coding regions

The non-coding region of the gene consists of promoter, 5 and 3 untranslated regions (5 UTRs, 3 UTRs), intron and intergenic regions. It was found that promoter region mutation had the greatest influence on gene expression, intron mutation generally caused alternative splicing, 5_and 3_UTRs and inter-gene region mutation affected gene transcription and translation efficiency.

The second nucleotide in intron 8 of the bovine ED1 gene mutated from G to T, causing bovine anhidrotic ectodermal dysplasia. The mutation results in the absence of a tumor Necro SIS factor (TNF) like domain at the C-terminal of the translated protein, which plays an important role in protein stability[26]. It was also found that the mutation of ED1 gene also affected the development of bovine mucous glands, and mucous gland dysplasia was one of the important characteristics of human sexually linked anhidrotic ectodermal dysplasia[27,28].

More than 2 gene related complex diseases

Some of the most economically important herd diseases, such as mastitis, brucellosis, reproductive disorders syndrome and other diseases are very complex causes, so also known as complex disease (**Figure 1**). The etiology of complex diseases mainly includes pathogenic microorganisms, environmental factors, animals themselves and the interaction between these factors. At present, these diseases are mainly controlled by strengthening management, quarantine, vaccination, pathogen control, treatment, isolation and slaughter. However, the effectiveness of these methods has been questioned, mainly because of drug residue problems in the treatment and prevention of drug use, and antibiotic abuse is liable to lead to increased drug resistance of pathogens[29,30]. Therefore, the selection of individuals with genetic resistance to diseases as seed is the key to the long-term effective control of such diseases[4,31,32].

Complex diseases involve the interaction of multiple genes, so the premise of selecting resistant individuals is to identify the polygenes or genetic markers that affect these diseases. Screening resistance-related genes and markers is mainly aimed at the correlation analysis between resistance traits and related candidate genes or molecular markers. In addition, the location of resistance-related quantitative trait loci (QTLs) is also an important method[31]. Much evidence has shown that mutations in innate and acquired immunity-related genes are closely associated with resistance to complex diseases[31,32].

2.1 Mastitis

Mastitis is one of the most common diseases in dairy cows, mainly caused by pathogenic bacteria such as Staphylococcus aureus, Streptococcus and Escherichia coli[32]. The disease not only reduces milk production and affects milk quality, but also increases the abortion rate and elimination rate of cows, which is the most serious economic loss of the dairy industry. Much research has been done on the resistance and susceptibility to mastitis, including immunity-related genes, antibody-related genes, neutrophil-related genes essential for innate resistance to infection, and T-cell differentiation-related genes[32–35].

When dairy cows suffer from mastitis, the migration of neutrophils to the sites of infection requires the participation of chemokine receptor CXCR2. It was found that there was a G777C SNP (GenBank login number: U19947) in the CXCR2 gene of dairy cows. The location of the SNP was closely related to calcium signal regulation and mobilization and G protein binding[35]. Further studies showed that the GG genotype of this SNP locus was significantly associated with recessive mastitis resistance in Holstein cows, while CC genotype was significantly associated with recessive mastitis susceptibility, but no such association was detected in clinical mastitis cows[36]. A study of CCR2, another chemokine receptor gene, in Holstein cattle herds in Canada showed somatic cell score.

Estimated breeding value (EBV) of SCS and breast depth were significantly correlated with C. 414C > T SNP of the gene[37]. Studies on Chinese Holstein herds showed that SNP g. 13598 C > T in the intron of CD4 gene was significantly associated with EBV in SCS, and the EBV in CC dairy cows was significantly higher than that in CT individuals[33]. These SNPs markers are significantly associated with the estimated breeding value of Mastitis-Related traits, and are important candidate genes for mastitis resistance breeding.

Molecular markers and QTLs with significant effects on mastitis resistance were also detected by genomic scanning[38,39] and QTL mapping[34,40]. These QTLs located in specific regions of the genome may contain actual genes or

mutations that affect mastitis resistance or susceptibility. For example, studies of three genes near a QTL (BTA29) affecting SCC showed that a 3-base insertion within the FEZL gene (neurodevelopmental-related transcription factor) led to the extension of glycine (12G) at position 12 to position 13 (13G)[34]. Further analysis showed that 12G FEZL might enhance the mastitis resistance of dairy cows, and the resistant individuals (12G) could promote the expression of axon molecule brain signal protein 5A (SEMA5A), and then induce the expression of nine immune-related genes including TNF-a and IL-8. However, the expression of the protein was reduced in susceptible individuals (13G). These results indicate that mastitis resistance is closely related to the transcriptional activity of FEZL gene.

2.2 Brucellosis

Brucellosis, also known as Mediterranean relaxing fever or Maltese fever, is a zoonotic infectious disease caused by Brucella. Its clinical features are long-term fever, hyperhidrosis, arthralgia and hepatosplenomegaly. It is reported that some individuals of mice, humans and cattle are naturally resistant to Brucella. Breeding resistant cattle can greatly enhance the resistance to Brucella in cattle. Studies on mice showed that NRAMP1 gene was associated with resistance or susceptibility to brucellosis[44]. Further studies on several cattle breeds and genetic patterns of brucellosis showed that there was a microsatellite marker of (GT) n in the non-coding region of NRAMP1 gene 3. Among them, individuals with GT13/GT13 genotype were resistant to brucellosis. The genotypes of GT14/GT14, GT13/GT14 or GT13/ GT15 were susceptible to[45,46]. But some studies also found that there was no significant correlation between NRAMP1 gene GT13 and bovine brucellosis resistance[47]. This suggests that there may be other genes associated with brucellosis resistance in the bovine genome.

2.3 Cattle tick infection

Bovine ticks are important parasites of the genus Bovine. They attach to the skin of cattle to absorb blood and secrete neurotoxins to paralyze cattle. They are important vectors of various infectious diseases (Texas bovine fever, microsporidiosis, hemorrhagic fever and encephalitis) of ruminants such as cattle. It was found that some individuals in the herd were resistant to ticks, and the host immune response was detected in different cattle breeds infected by B. minus and B. americana. Numerous studies have reported that N'Dama cattle and Bos. indicus cattle in West Africa are more tolerant to ticks than temperate cattle (Bos. taurus). Mast cells of host skin play a defensive role in the process of resistance to tick infection. The number of mast cells in the skin of tumor cattle with high tick resistance is twice that of temperate breeds[51]. According to Martinez *et al*.[52], the number of ticks in bovine body was significantly correlated with the alleles * 10 and * 42 of DRB 3.2 of bovine major histocompatibility complex (BoLA). DRB3.2 * 18, 20 and * 27 were associated with the low number of ticks, and alleles * 20 and * 27 were associated with the low number of ticks.*26 is also related, but the impact is relatively small. Obviously, the immune genes in cattle play an important role in enhancing the resistance to infection by cattle.

3. Genetic control of bovine diseases

Molecular genetic basis of cattle diseases provides a new and safe way for breeders to control diseases. Selecting resistant individuals and eliminating susceptible individuals through genetic breeding are beneficial genetic control methods for cattle herds, producers and consumers.

3.1 Select disease resistant individuals according to disease records.

In the same environment and under the same infection conditions, some individuals in the cattle have disease, some do not, non-disease individuals indicate that it may have disease resistance genes. Selecting, breeding and leaving offspring of such individuals can increase the number of disease-resistant individuals and increase the gene frequency of disease-resistance-related genes in cattle herds. This method is intuitive and simple, can take into account all resistance genes, but because of the low heritability of disease resistance, the selection effect is not easy to continue to consolidate, and only after the occurrence of disease can choose.

3.2 Select disease resistant individuals according to selection index.

In the dairy breeding work, some disease resistance has been selected as the main choice content into the selection index. The earliest example is the choice of dairy cattle disease resistance in countries such as northern Europe, Norway, Finland, Sweden and Denmark. In addition to choosing milk production, these countries pay special attention to the recording of disease treatment information, increasing the choice of mastitis, reproductive diseases, ketosis and other diseases. In Norway, because cows are too large, mastitis resistance includes only clinical mastitis information, Denmark uses somatic cell counts as an indicator of mastitis breeding values, while the Finnish and Swedish dairy breeding objectives include both traits. Most other regions and countries in the world, including China and the United States, have gradually added disease resistance traits to dairy cattle breeding objectives in the past 10 years. At present, dairy cattle breeding objectives mainly include longevity, health and reproductive traits (functional traits)[38] in addition to milk production traits.

3.3 Penetration of disease related genes

Infiltration of disease-resistance-related genes, i.e. gene infiltration, refers to the repeated backcrossing between a high-resistance variety and another low-resistance variety, resulting in the gradual infiltration of genes from high-resistance varieties into the gene pool of low-resistance varieties. Purposeful gene introgression is a long term.

The process, for example, in Australia over the past 30 years, has successfully infiltrated the blood of parasitic and heat-resistant Brahman cattle into the British common cattle breed[52] in the northern region by crossing and backcrossing.

3.4 Marker assisted selection for disease resistance

As mentioned earlier, with the completion of bovine genome sequencing and in-depth study, there is now more information and methods to mine and validate disease resistance-related genes, QTLs or molecular markers closely linked to them. In the long run, Marker as-sistant selection (MAS) is a good way to quantify the presence or absence, size or size of disease resistance, and then incorporate these disease resistance genes, QTLs or markers into existing selection schemes. The efficiency of marker-assisted selection for disease resistance depends on whether these genes or markers are the disease resistance genes themselves or are closely linked to them.

Single locus control disease MAS effect is better, through genetic testing from cattle to weed out individuals carrying mutation genes, can effectively limit the spread of such diseases. Such as control of bovine spinal deformity syndrome gene SLC35A3[8,53] and so on. However, MAS has not achieved significant results in the selection of complex diseases in cattle. The main reason is that most disease resistance is controlled by complex, less effective polygenes, but little is known about its genetic mechanism and molecular basis of related genes[32].

3.5 Genome selection for disease resistance

Disease resistance-related genes may involve a series of genes or molecular markers on each chromosome in the bovine genome. If we fit as many markers or genes as possible at the genome level into the selection index and carry out the genome selection (GS) of disease resistance, it is possible to improve the disease resistance of animals. Because the measurement index of complex disease resistance is difficult to define and varies greatly, there are not many studies in this area[54].

3.6 Epigenetic regulation of disease resistance

Compared with single locus-controlled genetic diseases, multilocus-controlled diseases are more complex, and the interactions between multigenes in the host become more complex due to pathogenic and environmental factors. Recent research results on epigenetic regulation of human complex diseases have greatly opened up a new way to study the disease resistance of livestock and poultry[55–57]. Epigenetics is the transmission of genetic information from individuals to their offspring through non-DNA sequences, including DNA methylation, histone modification, nucleosome remodeling, and small RNA expression. Epigenetics is one of the important mechanisms regulating organism-pathogen-environment interaction. Studies have found that epigenetic disorders cause a number of major human and animal diseases[55–59].

The common mechanism of genetic resistance to complex diseases needs to be studied. In conclusion, the genetic basis of single locus control of cattle diseases is relatively simple, and can be effectively controlled by molecular genetic techniques and methods. In contrast, the discovery and application of genetic variations in complex diseases are challenging, and it is of great significance to discover genetic variations and molecular markers associated with resistance/susceptibility to complex diseases in cattle. In genomics, epigenomics, proteomics and protein-DNA interactions, the development of detection and analysis techniques based on microarrays and high-throughput sequencing will promote the discovery and application of genes related to resistance to complex bovine diseases.

References

1. feuk l, marshall cr, wintle rf, scherer sw. structural variants: changing the landscape of chromosomes and de - sign of disease studies. hum mol genet, 2006, 15 (suppl. 1): r57–r66.
2. stothard p, choi jw, basu u, sumner - thomson jm, meng y, liao xp, moore ss. whole genome resequenc - ing of black angus and holstein cattle for snp and cnv discovery. bmc genomics, 2011, 12: 559.
3. check e. human genomes: patchwork people. nature, 2005, 437 (7062): 1084–1086.
4. ibeagha - awemu em, kgwatalala p, ibeagha ae, zhao x. a critical analysis of disease associated dna polymor - phisms in the genes of cattle, goat, sheep and pig. mamm genomes, 2008, 19 (4): 226–245.
5. nagahata h t, nishiyama, kanae y, higuchi h, kawai k, endoh d, hayashi m, kurosawa t. a retrospective survey of the development of complex in moscow and other cities malformation car riers in 9 holstein dairy herds in hokkaido, japan. j vet med sci, 2009, 71 (6): 793–795.
6. cherel p, gl énisson j, figwer p, pires j, damon m, - m, le roy p. updated estimates of hal n and rn - effects on pork quality: fresh and processed far and ham. meat science, 2010, 86 (4): 949–954.
7. cartegni l, chew sl, krainer acres. listening to silence and understanding nonsense: exonic mutations that affect splicing. nat rev genet, 2002, 3 (4): 285–298.
8. thomsen b, horn, p, panitz f, bendixen e, petersen ah, holm le, nielsen $agerholm js, arnbjerg j, bendixen c. a mis- sense mutation in the bovine slc35a3 gene, encoding a udp - n - acetylglucosamine transporter, causes malfor- mation complex in moscow and other cities. genome res, 2006,16 (1): 97–105.
9. shuster de, kehrli me jr, ackermann, mr. gilbert ro. identification and development of a genetic defect that causes leukocyte adhesion deficiency in holstein cattle. proc natl acad sci usa, 1992, 89 (19): 9225–9229.
10. protection, scharfenstein m, brenig b. implication of com - plex moscow and other cities malformation and bovine leukocyte adhe the deficiency dna based testing on disease frequency in the holstein population. j dairy sci, 2008, 91 (12): 4854–4859.
11. sun dx, fan xh, xie y, chu q, sun y, zhang y, zhang sl, gong wj, chen sh, li yh, shi wh, zhang y. short communica- tion: distribution of recessive genetic defect carriers in chinese holstein. j dairy sci, 2011, 94 (11): 5695–5698.
12. meydan h, yildiz ma, agerholm js. screening for bo vine leukocyte adhesion deficiency, deficiency of uridine monophosphate synthase complex in moscow and other cities, malformation, bovine citrullinaemia, and factor xi deficiency in holstein cows reared in turkey. acta vet scand, 2010, 52 (1): 56.
13. pierce kd, handford ca, morris r, vafa b, dennis, healy pj, schofield pr. a nonsense mutation in the α1 subunit 0 of the glycine receptor associated with bovine myoclonus. mol cell neurosci, 2001, 17 (2): 354–
363.
14. leipprandt jr, chen h, horvath, qiao xt, jones mz, friderici kh. identification of a bovine beta mannosidosismutation and detection of two beta mannosidase pseudogenes. mamm genomes, 1999, 10 (12): 1137–1141.
15. schwenger b, sch öber, simon d. dumps cattle carry a point mutation in the uridine monophosphate synthase gene. genomics, 1993, 16 (1): 241–244.
16. tollersrud ok, mountain, healy p, evjen g, ramachandran u, nilssen Ø. purification of bovine lysosomal a man nosidase, characterization of its gene and determination of two mutations that cause a - mannosidosis. eur j bio- chem, 1997, 246 (2): 410–419.
17. dennis yes, healy pj. definition of the mutation responsi for maple syrup urine disease - t in poll shorthorns and genotyping poll shorthorns and poll for maple syrup urine disease alleles all about herefords. res vet sci, 1999, 67 (1): 1–6.
18. zhang b, healy pj, crabb dw, harris ra. premature translation termination of the pre - subunit e1 of the branched chain alpha ketoacid dehydrogenase as a cause of maple syrup urine disease in polled hereford calves. j biol chem, 1990, 265 (5): 2425–2427.
19. dennis yes, moran c, healy pj. the bovine alpha glucosidase gene, coding region, genomic structure, and mutations that cause bovine generalized glycogenosis. mamm genomes, 2000, 11 (3): 206–212.
20. colige a, sieron al, li sw, black u, petty, wertelecki w, wilcox w, krakow d, cohn ie, reardon w, byers ph, lapi ère cm, prockop dj, nusgens bv. human ehlers danlos syndrome type vii c and bovine dermatosparaxis are caused by muta- tions in the procolla gene i n - proteinase genes. the j hum genet, 1999, 65 (2): 308–317.
21. hirano t, hirotsune s, sasaki s, kikuchi t, sugimoto y. a new deletion mutation in bovine claudin - 16 (cl - 16) defi- ciency and diagnosis. anim genet, 2002, 33 (2): 118–122.

22. Sugiyama A, Ozaki K, Miyazaki, Tanabe Y, Takeuchi T, Narama I. Renal dysplasia unrelated to claudin-16 deficiency in Japanese Black cattle. J Comp Pathol, 2007, 137(1): 71–77.
23. Watanabe D, Hirano T, Sugimoto Y, Ogata Y, Abe S, Ando T, Ohtsuka H, Kunieda T, Kawamura S. Carrier rate of Factor XI deficiency in stunted Japanese black cattle. J Vet Med Sci, 2006, 68(12): 1251–1255.
24. Sugimoto M, Furuoka H, Sugimoto Y. Deletion of one of the duplicated HSP70 genes causes hereditary myopathy of diaphragmatic muscles in Holstein-Friesian cattle. Anim Genet, 2003, 34(3): 191–197.
25. Kawakura K, Miyake YI, Murakami RK, Kondoh S,Hirata TI, Kaneda Y. Deletion of the SRY region on the Y chromosome detected in bovine gonadal hypoplasia (XY female) by PCR. Cytogenet Cell Genet, 1996, 72(2 3): 183–184.
26. Drögemüller C, Peters M, Pohlenz J, Distl O, Leeb T. A single point mutation within the ED1 gene disrupts correct splicing at two different splice sites and leads to anhidrotic ectodermal dysplasia in cattle. J Mol Med, 2002, 80(5): 319–323.
27. Seeliger F, Drögenmüller C, Tegtmeier P, Baumgärtner W, Distl O, Leeb T. Ectodysplasin-1 deficiency in a German Holstein bull associated with loss of respiratory mucous glands and chronic rhinotracheities. J Comp Pathol, 2005, 132(4): 346–349.
28. Aqino A, Kohama N, Ishikawa S, Tomita K, Nonaka S, Shimizu K, Tanabe Y, Okawa H, Morita M. A novel mutation of the bovine EDA gene associated with anhidrotic ectodermal dysplasia in Holstein. Hereditas, 2011, 148(1): 46–49.
29. Vanderhaeghen W, Hermans K, Haesebrouck F, Butaye P. Methicillin-resistant Staphylococcus aureus (MRSA) in food production animals. Epidemiol Infect, 2010, 138(5): 606–625.
30. Köck R, Siam K, Al-Malat S, Christmann J, Schaumburg F, Becker K, Friedrich AW. Characteristics of hospital pa- tients colonized with livestock-associated meticillin-resistant Staphylococcus aureus (MRSA) CC398 versus other MRSA clones. J Hosp Infect, 2011, 79(4): 292–296.
31. Berry DP, Bermingham ML, Good M, More SJ. Genetics of animal health and disease in cattle. Ir Vet J, 2011, 64(1): 5.
32. Mulder HA, Lidauer MH, Vilkki JH, Strandén I, Veer- kamp RF. Marker-assisted breeding value estimation for mastitis resistance in Finnish Ayrshire cattle. J Dairy Sci, 2011, 94(8): 4164–4173.
33. He YH, Chu Q, Ma PP, Wang Y, Zhang Q, Sun DX, Zhang Y, Yu Y, Zhang Y. Association of bovine CD4 and STAT5b single nucleotide polymorphisms with somatic cell scores and milk production traits in Chinese Holsteins. J Dairy Res, 2011, 78(2): 242–249.
34. Sugimoto M, Fujikawa A, Womack JE, Sugimoto Y. Evi- dence that bovine forebrain embryonic zinc finger-like gene influences immune response associated with mastitis resistance. Proc Natl Acad Sci USA, 2006, 103(17): 6454–6459.
35. Grosse WM, Kappes SM, Laegreid WW, Keele JW, Chitko- McKown CG, Heaton MP. Single nucleotide polymor-phism (SNP) discovery and linkage mapping of bovine cytokine genes. Mamm Genome, 1999, 10(11): 1062–1069.
36. Youngerman SM, Saxton AM, Oliver SP, Pighetti GM. Association of CXCR2 polymorphisms with subclinical and clinical mastitis in dairy cattle. J Dairy Sci, 2004, 87(8): 2442–2448.
37. Leyva-Baca I, Schenkel F, Sharma BS, Jansen GB, Karrow NA. Identification of single nucleotide polymorphisms in the bovine CCL2, IL8, CCR2 and IL8RA genes and their association with health and production in Cana- dian Holsteins. Anim Genet, 2007, 38(3): 198–202.
38. Rupp R, Boichard D. Genetics of resistance to mastitis in dairy cattle. Vet Res, 2003, 34(5): 671–688.
39. Ogorevc J, Kunej T, Razpet A, Dovc P. Database of cattle candidate genes and genetic markers for milk production and mastitis. Anim Genet, 2009, 40(6): 832–851.
40. Khatar MS, Thomson PC, Tammen I, Raadsma HW. Quantitative trait loci mapping in dairy cattle: review and meta-analysis. Gen Sel Evol, 2004, 36(2): 163–190.
41. Montaraz JA, Winter AJ. Comparison of living and nonliving vaccines for Brucella abortus in BALB/c mice. Infect Immun, 1986, 53(2): 245–251.
42. Templeton JW, Estes DM, Price RE, Smith R III, Adams LG. Immunogenetics of natural resistance to bovine brucellosis. In: Teal A, ed. Proceedings of the 4th World Congress of Genetics. Applied to Livestock Production. Edinburgh: University of Edinburgh, 1990:. 396–399.
43. Carvalho Neta AV, Stynen APR, Paixão TA, Miranda KL, Silva FL, Roux CM, Tsolis RM, Everts RE, Lewin HA, Adams LG, Carvalho AF, Lage AP, Santos RL. Modulation of the bovine trophoblastic innate immune response by Brucella abortus. Infect Immun, 2008, 76(5): 1897–1907.
44. Vidal SM, Malo D, Vogan K, Skamene E, Gros P. Natural resistance to infection with intracellular parasites: isolation of a candidate for Bcg. Cell, 1993, 73(3): 469–485.
45. Adams LG, Templeton JW. Genetic resistance to bacterial diseases of animals. Rev Sci Tech, 1998, 17(1): 200–219.
46. Paixão TA, Ferreira C, Borges ÁM, Oliveira DAA, Lage AP, Santos RL. Frequency of bovine Nramp1 (Slcla1) alleles in Holstein and Zebu breeds. Vet Immunol Im- munopathol, 2006, 109(1–2): 37–42.
47. Paixão TA, Poester FP, Carvalho Neta AV, Borges ÁM, Lage AP, Santos RL. NRAMP1 3' untranslated region

polymorphisms are not associated with natural resistance to Brucella abortus in cattle. Infect Immun, 2007, 75(5): 2493–2499.
48. Morris CA. A review of genetic resistance to disease inBos taurus cattle. Vet J, 2007, 174(3): 481–491.
49. Almazán C, Lagunes R, Villar M, Canales M, Rosario- Cruz R, Jongejan F, de la Fuente J. Identification and characterization of Rhipicephalus (Boophilus) microplus candidate protective antigens for the control of cattle tick infestations. Parasitol Res, 2010, 106(2): 471–479.
52. Engracia Filho JR, Bechara GH, Teodoro RL. Dermal mast cell counts in F2 Holstein Gir crossbred cattle artifi- cially infested with the tick Boophilus microplus (Acari: Ixodidae). Ann N Y Acad Sci, 2006, 1081: 476–478.
51. Martinez ML, Machado MA, Nascimento CS, Silva MVGB, Teodoro RL, Furlong J, Prata MC, Campos AL, Guimarães MF, Azevedo AL, Pires MF, Verneque RS. As- sociation of BoLA-DRB3.2 alleles with tick (Boophilus microplus) resistance in cattle. Genet Mol Biol, 2006, 5(3): 513–524.
52. Almazán C, Lagunes R, Villar M, Canales M, Rosario- Cruz R, Jongejan F, de la Fuente J. Identification and characterization of Rhipicephalus (Boophilus) microplus candidate protective antigens for the control of cattle tick infestations. Parasitol Res, 2010, 106(2): 471–479.
53. Chu Q, Zhang Y, Sun DX, Yu Y, Wang YC, Zhang Y. Iden- tification of the complex vertebral malformation gene in Chinese Holstein and its association with dairy perform-ance traits. Hereditas, 2010, 32(7): 732–736.
54. Maceachern S, Muir WM, Crosby SD, Cheng HH. Genome-wide identification and quantification of cis-and trans-regulated genes responding to Marek's disease virus infection via analysis of allele-specific expression. Front Genet, 2011, 2: 113.
55. Egger G, Liang GN, Aparicio A, Jones PA. Epigenetics in human disease and prospects for epigenetic therapy. Na- ture, 2004, 429(6990): 457–463.
56. Yu Y, Zhang HM, Tian F, Zhang WS, Fang HB, Song JZ. An integrated epigenetic and genetic analysis of DNA methyltransferase genes (DNMTs) in tumor resistant and susceptible chicken lines. PLoS ONE, 2008, 3(7): e2672.
57. Durham A, Chou PC, Kirkham P, Adcock IM. Epigenetics in asthma and other inflammatory lung diseases. Epige- nomics, 2010, 2(4): 523–537.
58. Luo J, Yu Y, Song J. Epigenetics and Animal Health. In: Khatib H. Livestock Epigenetics. Oxford, UK: Wiley-Blackwell.
59. He YH, Yu Y, Zhang Y, Song JZ, Mitra A, Zhang Y, Wang YC, Sun DX, Zhang SL. Genome-wide bovine H3K27me3 modifications and the regulatory effects on genes expressions in peripheral blood lymphocytes. PLoS ONE, 2012, 7(6): e39034