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MODEL OF SENSITIVITY CATTLE TO MASTITIS ON THE BASIS OF LYMPHOCYTIC AND MOLECULAR GENETIC MARKERS

Abstract

Mastitis of cows causes significant harm to dairy farming, a susceptibility to which is partly determined by genetic factors. Therefore, identifying the susceptibility or resistance of cows to mastitis at an early stage of postnatal ontogenesis has both practical and scientific importance.

In this work, we examined a model grounded on the collegial use of lymphocyte antigens class I MHC cattle and DNA markers based on alleles BoLA-DRB3 gene to identify the sensitivity of heifers to mastitis to their use in a milking herd.

On the data of testing of 649 cows of the Ukrainian black-and-white breed, the antigens of histocompatibility were revealed, and the statusmetric model facilitated determining the integral estimation of sensitiveness (Z) to mastitis was constructed. The greater the positive Z value, the higher the predicted resistance to mastitis and vice versa. The model yields 69.2% correct mastitis susceptibility decisions based on 17 class I antigens (antigens W2, W6, W31, W14, W19, W15, A9, A12, A13 and A24 indicate susceptibility and W10, A1, A3, A6, A16, A17 and A22 – indicate resistance to the disease).

*Some exon 2 alleles of the BoLA-DRB3 gene were found to be associated with mastitis. For 162 cows from the preliminary sample DRB3.2*18, *24, *26 and *48 alleles characterize susceptibility to mastitis, and BoLA-DRB3.2*08, *13 and *22 – characterize resistance to the disease.*

A comparative analysis of the association of lymphocyte and DNA-markers was performed by comparing the diagnosis, status score, and the presence of associated alleles in the genotype. Two of the four possible variants unambiguously indicate the immune status of the cow:

– diagnosis and integral score (by sign) coincide, and there is an allele in the genotype that coincides with the established diagnosis (65,7%);

– diagnosis and integral score sign do not coincide, and there is a DNA marker in the genotype that coincides with the immune status of the animal by Z (13,3%).

For 83 animals out of 105 in which DNA markers were detected, the immune status established by the statusmetric model was confirmed, for a total of 79%. The accuracy in predicting the susceptibility of cows to mastitis increased by 9.8%.

Following the obtained results, the model for predicting sensitivity of heifers of Ukrainian black-and-white breed to mastitis at the stage of early postembryonic ontogenesis has been proposed. The model is universal and can be applied to different cattle breeds after appropriate research.

Key words: *mastitis, cattle, major histocompatibility complex, lymphocytic antigens, BoLA-DRB3 gene, alleles, polymorphism, DNA marker.*

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Introduction. The main concern of veterinary medicine specialists is how to protect farm animals from diseases and preserve profitable traits. The answer to this question can be provided by identifying the BoLA system markers associated with bovine diseases and, above all, the possibility of their cost-effective use in practice.

The productivity of a dairy herd depends on many factors: heredity (genetics), pedigree, physiological condition, and feeding and housing conditions of cows. Diseases are among the key factors minimizing milk yield and milk quality. The biggest problems in dairy farming are related to mastitis. An estimate of the incidence of mastitis worldwide shows that the disease is diagnosed in 48 cows out of every 100 head, of which 39 have a subclinical course of the disease and 9 animals have a clinical course. The damage caused by mastitis is estimated as significant, ranging from 0.0388 to 0.0428 kg of milk per day. Udder disease leads not only to milk loss but also culling of animals. In parallel, treatment costs increase [1]. Mastitis is a costly disease. Estimates of economic losses from clinical mastitis range from €61 to €97 per cow [2].

Susceptibility to mastitis is assessed at the stage of the productive use of animals. This requires observation of the cow over several lactations. Several studies point to a genetic basis of cow susceptibility to mastitis [3]. To reduce the risk of mastitis, animals genetically resistant to udder disease should be included in the working herd by finding markers of susceptibility to mastitis and hence selecting cows in the main herd before they become productive.

Immune status is the overall resultant activity of genes that determine cellular and humoral immunity factors and the same type of immune reactivity strength for a broad group of antigens. One of the main points about the immune status of the body is the presence of natural genetically determined markers which can be used to test and predict future reactivity [4]. To date, two types of biological activity have been identified which are related to the immunological reactivity of the body as a whole and the role played by histocompatibility antigens in intercellular interactions. There is evidence that the immune response is determined by genes located in the same region of the major histocompatibility complex (MHC) as the histocompatibility genes.

The nature of the relationship between tissue antigens of an individual and its propensity for pathology is primarily established by the genetic association of loci controlling the antigenic composition of tissues and functional specificity of immunocompetent cells, which is the main factor responsible for the propensity for disease.

There are two types of MHC linkages to diseases:

– linkage of disease and MHC (class I locus) loci located on the same chromosome;

– structural construction of class II genes responsible for disease susceptibility.

A genetic marker is a DNA polymorphism that can be readily identified by molecular or phenotypic analysis. The development of molecular research methods makes it possible to create new test systems which allow for the analysis of genetic polymorphism at the level of gene products (protein or biochemical polymorphism) and at the level of cellular genetic material (DNA polymorphism). MHC antigens and genetic markers (certain gene alleles) are used as polymorphic markers when studying their associations with multifactorial diseases [5].

One of the main points about immune status is the presence of natural genetically determined markers in the body, which can determine and predict the oncoming reactivity of a biological entity. Consequently, it should be assumed that any immunological system can be regarded as a biological marker possessing properties intrinsic to lymphocytes, that is, those properties with which the organism is born and unrelated to the previous in vivo sensitization of organisms. Such markers include MHC antigens [6].

Marker systems of polymorphic DNA nucleotide sequences make it possible to test genetic polymorphism directly at the gene level. DNA markers are universal, which allows us to solve the problem of saturating the genome with markers and tag almost any region of DNA. A large number of different types of DNA markers based on single nucleotide substitutions (SNPs) have been developed [7]. They are inherited in accordance with Mendelian laws, represented by a significant number of alleles, are not influenced by environmental factors, and there is no pleiotropy for profitable traits.

When selecting a marker for genetic studies, the informative value and individual level of typing difficulty must be taken into account. In this context, the BoLA-DRB3 gene encoding MHC class II antigens is quite attractive. Particular attention is paid to exon 2 of this gene, which is the most polymorphic among all MHC loci.

Analysis of recent research and publications. Class I lymphocyte antigens and BoLA-DRB3 gene alleles are used to detect disease susceptibility or resistance associations, including mastitis.

Studies of Slovak gray cows proved a positive association of W6 antigen with susceptibility and W20 with resistance to mammary gland disease [10]. In Norwegian cattle, a positive association of W11 and W16 antigens with mastitis were found, whereas the W2 antigen characterizes resistance to the disease [11; 12].

Tissue typing methods are based on an antigen-antibody serological reaction that occurs between lymphocytes carrying antigenic determinants and an isoimmune serum containing antibodies to BoLA antigens. Eleven monospecific and more than two dozen oligo-specific sera are used to identify BoLA antigens, which theoretically allows more than 30 antigens to be identified in a single animal. Statusimetric is applied to identify “significant” antigens [18].

Thus, the study of the Kostroma breed revealed a significant association of antigens MSU A3, A15, A18, W10 and W31 with acceptability, and antigens W8, W19 and MSU A1 with resistance to mastitis [8; 9].

Many contributions were devoted to the search for DNA markers based on BoLA-DRB3.2 alleles associated with mastitis susceptibility. Thus, in a study of Holstein cattle, the BoLA-DRB3.2*03 allele had a statistically significant association with resistance and the *08 allele with susceptibility to clinical mastitis [13]. In the Norwegian red breed,

the *22 and *26 alleles were associated with the risk of clinical mastitis, whereas a whole group of *07, *11, *18 and *24 alleles had a strong association with resistance [14]. Significant associations were found with susceptibility to mastitis in Japanese Holsteinized cows that had *08 and *16 alleles in the genotype and disease resistance in the presence of alleles 22, *23 and *24 [15].

A study of exon 2 polymorphism of the BoLA-DRB3 gene and associations with mammary disease susceptibility of its alleles in domestic breeds identified DNA markers in three breeds: Ukrainian black-and-white milk (predisposition – *24, *26, resistance – *13, *22), Ukrainian red-and-white milk (predisposition – *07, *08, resistance – *22, *24), Ukrainian white-headed (predisposition – *24, resistance – *22) [16; 17].

Purpose. Any method of assessing the immunogenetic status of a separate animal on based on markers discovered following the results of population analysis is always characterized by a certain accuracy. It is necessary to look for ways to increase the accuracy of forecasting. Considering that mastitis has a fairly wide range of causes of the disease, and Class I antigens and alleles of the BoLA-DRB3.2 gene are responsible for the functioning of various branches of immunity, it is logical to elaborate a method (model) for evaluating immunogenetic status which takes into account the analysis results of both types. In this case, it is expected that the accuracy of predicting sensitivity to the heifer at the early stage of postnatal ontogenesis will increase.

Methodology. The study included 649 cows of Ukrainian black-and-white milk breed.

Histocompatibility antigens were determined by a two-step cytotoxic test in a Kissmeyer-Nielson microvariant modified for cattle [19; 20]. The immunogenetic status of the animals was assessed using a statusmetric model [18] developed by relyion on the class I histocompatibility antigen base, which was identified by serological analysis of 32 antilymphocyte serum.

The disease susceptibility score is considered according to a first-degree polynomial:

$$Z = B_0 + B_1A_1 + B_2A_2 + \ldots + B_nA_n = B_0 + \sum_{i=1}^{n} B_iA_i, \quad (1)$$

where Z – integral estimation;
A_i – BoLA antigens;
B_i – coefficient of influence of indicator A_i on the value Z (impact factor);
n – number of indicators.

The values of the impact factor have different signs and magnitudes. A sign near it indicates a negative (susceptibility) or positive (resistance) effect of the antigen on the cow's sensitivity to mastitis. The absolute value of B_i determines the degree of influence of a given attribute on the value of Z. The greater the value of the coefficient, the more weighted the effect of the antigen on the value of the integral score. If no antigen is found, the corresponding value of $A_i = 0$, otherwise $A_i = 1$.

For the two alternative states, the Z scale has three regions: zone to the left of α1 (integral score value $Z < \alpha_1$) – determines the propensity for mastitis; zone to the right of α_2 (integral score value $Z > \alpha_2$) – resistance; between the values of α_1 and α_2 there is a region of uncertain states (fig. 1).

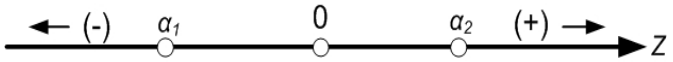

Fig. 1. A univariate scale of object states for two alternatives:
α_1, α_2 - conditional units of the object state; (−) and (+) – a zone of adverse and favorable states, respectively

This model allows for the selection of mastitis-resistant heifers based on integral estimation after typing the animal by antigens.

The study of allelic diversity was carried out involving a sample of 162 cows for which BoLA-antigens were previously tested. The BoLA-DRB3.2 gene allele polymorphism was determined via the restriction analysis of amplification products (PCR-RFLP) and allele-specific PCR (AS-PCR) with primers ER-17 and VD-19 and HLO-07 and HLO-24D [21]. DNA markers associated with sensitivity to mastitis are established by the magnitude of the relative risk (*RR*), which identifies the likelihood of the disease progress in antigen animal carriers compared to those who have not one. The degree of reliability was monitored by test χ^2 [16]. Calculations conducted using the Microsoft Office Excel 2003 package and separate Statistica 6.0 package applications for Windows.

Results and discussion. The statusmetric method makes it possible to implement an individual approach to assessing the sensitivity of an animal to the disease. The antigen carries information about the association of the gene with the disease. Such information will always be insufficient to judge the likelihood of disease in postnatal ontogeny. If there is a set of features (markers) through a set of BoLA antigens, then the probability of such a judgment will be much higher. The transition from the analysis of the effect of individual antigens to the analysis of the animal's condition as a whole is realizedthrough statusmetric.

Treatment of the antigenic spectrum of a sample of 649 cows of the Ukrainian black-and-white dairy breed made it possible to obtain the following linear model for an integral assessment of sensitivity to mastitis [22]:

$$\boldsymbol{Z} = 0{,}599 - 1{,}556\mathbf{W2} - 1{,}133\mathbf{W6} + 0{,}747\mathbf{W10} - 0{,}563\mathbf{W31} - 0{,}33\mathbf{W14} - 0{,}657\mathbf{W19} - 0{,}695\mathbf{W15} + 0{,}231\mathbf{A1} + 0{,}387\mathbf{A3} + 0{,}799\mathbf{A6} - 0{,}685\mathbf{A9} - 0{,}285\mathbf{A12} - 0{,}619\mathbf{A13} + 0{,}332\mathbf{A16} + 1{,}121\mathbf{A17} + 0{,}447\mathbf{A22} - 0{,}244\mathbf{A24.}$$

For the alternative of "healthy-diseased" on the Z scale, the units of the condition of the object $\alpha_1 = -0{,}075$ and $\alpha_2 = 0{,}188$. When $Z < -0{,}075$ animal is susceptible to mastitis, with $Z > 0{,}188$ – resistant. If $-0{,}075 \le Z \le 0{,}188$ the decision is uncertain.

The model provides 69.2% of correct decisions on the sensitivity of Ukrainian black-and-white milk breed cows to mastitis, if an individual set of 17 BoLA class I antigens for each animal is known. The presence of error is due to the accuracy of the statusmetric model, as well as the alternativity of the object state, which consists in the availability of two stable variants of the system (the cow can be sick or healthy) and the lack of intermediate states of the object. Given the variety of input factors driving the occurrence of breast pathologies, the error in any model aimed at identifying predictive stochastic relationships in the stages of further development of the system can reach significant values.

A logical question seems to be whether it is possible to reduce the error of the statusmetric model to increase the accuracy of predicting heifer mastitis sensitivity before it is used in a milking herd. Alternatively, let's consider the use of BoLA-DRB3.2 gene alleles as DNA markers.

Studies of BoLA-DRB3 gene polymorphism in a sample of 162 cows revealed 7 candidate alleles for DNA markers of sensitivity to mastitis: BoLA-DRB3.2*18, *24, *26, *48 alleles characterize susceptibility to mastitis and BoLA-DRB3.2*08, *13, *22 – demonstrate disease resistance [16].

A comparative analysis of the communication of lymphocytic and DNA markers is carried out by comparing diagnosis, assessment states and the presence of DNA markers in the genotype.

Comparison of the diagnosis, integral assessment and availability/absence in the DNA marker genotype give the following analysis options:

1. The diagnosis and integral score (by sign) coincide, and there is an allele in the genotype that coincides with the established diagnosis – direct confirmation of immune status.

2. The diagnosis and the sign of the integral score do not match, and there is a DNA marker in the genotype that matches the immune status of the animal by Z – indirect confirmation of status by integral score.

3. The diagnosis and integral score marker is the same, and there is a DNA marker in the genotype indicating the opposite immune status with respect to the initial diagnosis − an uncertain situation.

4. There are no DNA markers or antagonists in the animal's genotype – no decision can be made.

Of the 162 cows tested, 105 had DNA markers in their genotype (table 1).

Variants 1 (65.7%) and 2 (13.3%) were confirmed for 83 animals, representing 79%. The accuracy in predicting susceptibility of cows to mastitis increased by 9,8% compared to the results of the statusmetric model.

Table 1. Clarification of diagnosis using BoLA-DRB3.2 gene alleles

<table>
<tr><th colspan="4">DNA markers</th><th colspan="5">Analysis data (%)</th></tr>
<tr><th rowspan="2">link by mastitis</th><th rowspan="2">alleles</th><th rowspan="2">number</th><th rowspan="2">in total</th><th colspan="2">number cows</th><th rowspan="2">direct confirmation</th><th rowspan="2">indirect confirmation</th><th rowspan="2">uncertainty</th></tr>
<tr><th>with markers</th><th>without markers</th></tr>
<tr><td rowspan="3">resistant</td><td>13*</td><td>17</td><td rowspan="3">80</td><td rowspan="8">105 (64,8)</td><td rowspan="8">57 (35,2)</td><td rowspan="4">69 (65,7)</td><td rowspan="4">14 (13,3)</td><td rowspan="8">22 (21,0)</td></tr>
<tr><td>22*</td><td>39</td></tr>
<tr><td>08*</td><td>24</td></tr>
<tr><td rowspan="5">susceptibility</td><td>24*</td><td>38</td><td rowspan="5">68</td></tr>
<tr><td>26*</td><td>14</td></tr>
<tr><td>18*</td><td>8</td><td colspan="2" rowspan="2">83 (79,0)</td></tr>
<tr><td>48*</td><td>8</td></tr>
</table>

Considering the obtained results, the following model for predicting the sensitivity of heifers of Ukrainian black-and-white milk breed to mastitis at the stage of early postembryonic ontogenesis is proposed:

1. Carry out heifer testing for class I lymphocyte antigens: W2, W6, W10, W31, W14, W19, W15, A1, A3, A6, A9, A12, A13, A16, A17, A22 and A24.

2. Find the value of the integral estimate Z.

3. If $Z < -0{,}075$ – the animal belongs to the group of cows with high risk of mastitis when used in a milking herd.

4. If $Z > 0{,}188$, the animal belongs to a group of cows at low risk of mastitis in the future.

5. If $-0{,}075 \le Z \le 0{,}188$, the animal should be tested for the presence of BoLA-DRB3.2 gene alleles.

5.1. If alleles *18, *24, *26 or (and) *48 are present in the heifer genotype, she should be placed in the high-risk group.

5.2. If alleles *08, *13 or (and) *22 are present in the heifer genotype, she should be placed in a low-risk group.

5.3. If there are no DNA markers in the heifer genotype or antagonist DNA markers are present, the animal is transferred to an undetermined risk group in which a continuous monitoring regime for possible homeostasis deviations from the norm should be established.

Conclusions and suggestions. Predicting the individual susceptibility of each individual animal to mammary gland disease at an early stage of postnatal ontogenesis is of great knowledge, because mastitis causes the greatest damage to the dairy industry. Accurate prediction will allow forming groups of cow resistant to mastitis by limiting the use of genetically prone to mastitis heifers in the milking herd.

The model considered in the work, in which lymphocytic markers on the basis of BoLA class I antigens and molecular-genetic markers on the basis of exon 2 alleles of BoLA-DRB3 gene, encoding the class II antigens, are used simultaneously to predict sensitivity of Ukrainian black-and-white milk cows to mastitis. It contributes to rendering 79% correct decisions on the immune status of the heifer in relation to sensitivity to mastitis.

The proposed model for predicting sensitivity to mastitis early in postnatal ontogenesis can be used for any cattle breed. This requires appropriate studies to identify class I antigens, develop a statusmetric model, and determine the BoLA-DRB3 gene polymorphism to establish DNA markers.

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МОДЕЛЬ ЧУТЛИВОСТІ ВЕЛИКОЇ РОГАТОЇ ХУДОБИ ДО МАСТИТІВ НА ОСНОВІ ЛІМФОЦИТАРНИХ І МОЛЕКУЛЯРНО-ГЕНЕТИЧНИХ МАРКЕРІВ

Анотація

Мастити корів, чутливість до яких частково зумовлена генетичними чинниками, завдають значної шкоди молочному скотарству. Тому виявлення сприйнятливості чи резистентності корів до маститу на ранньому етапі постнатального онтогенезу має як практичне, так і наукове значення.

У роботі розглянуто модель, яка базується на колегіальному використанні лімфоцитарних антигенів класу I ГКГ ВРХ і ДНК-маркерів на основі алелів гена для виявлення чутливості теличок до маститу до використання їх у дійному стаді.

За даними тестування 649 корів української чорно-рябої молочної породи виявлено антигени гістосумісності та побудовано статусметричну модель, за якою визначається інтегральна оцінка чутливості (Z) до маститу. Чим більше позитивне значення Z, тим вища прогнозована стійкість до маститу і навпаки. Модель дозволяє отримати 69,2% правильних рішень про чутливість до маститу на основі 17 антигенів класу I (антигени W2, W6, W31, W14, W19, W15, A9, A12, A13 і A24 вказують на схильність, а антигени W10, A1, A3, A6, A16, A17 і A22 – на резистентність до захворювання).

*Для 162 корів із попередньої вибірки виявлено алелі екзону 2 гена BoLA-DRB3 асоційовані з маститами: алелі DRB3.2*18, *24, *26 і *48 характеризують сприйнятливість до маститу, а алелі BoLA-DRB3.2*08, *13 і *22 – стійкість до захворювання.*

Порівняльний аналіз зв'язку лімфоцитарних і ДНК-маркерів проведено шляхом зіставлення діагнозу, статусметричної оцінки та наявності в генотипі асоційованих алелів. Два із чотирьох можливих варіантів однозначно вказують на імунний статус корови:

– діагноз та інтегральна оцінка (за знаком) збігаються, а в генотипі наявний алель, який збігається з установленим діагнозом (65,7%);

– діагноз і знак інтегральної оцінки не збігаються, а в генотипі наявний ДНК-маркер, який збігається з імунним статусом тварини за Z (13,3%).

Для 83 тварин зі 105, у яких було виявлено ДНК-маркери, підтверджено імунний статус, установлений за стаутусметричною моделлю, що сумарно становить 79%. Точність прогнозування чутливості корів до маститу зросла на 9,8%.

На основі отриманих результатів запропоновано модель для прогнозування чутливості теличок української чорно-рябої молочної породи до маститу на етапі раннього постембріонального онтогенезу. Модель має універсальний характер і після відповідних досліджень може застосовуватись до різних порід великої рогатої худоби.

Ключові слова: *мастит, велика рогата худоба, головний комплекс гістосумісності, лімфоцитарні антигени, ген BoLA-DRB3, алелі, поліморфізм, ДНК-маркер.*