Genetic analysis of leukosis incidence in United States Holstein and Jersey populations

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ABSTRACT

Bovine leukosis (BL) is a retroviral disease caused by the bovine leukosis virus that affects only cattle. It is associated with decreased milk production and increased cull rates due to development of lymphosarcoma. The virus also affects the immune system. Infected cows display a weak response to some vaccinations. It is important to determine if the heritability of BL susceptibility is greater than zero, or if the environment is the only factor that can be used to reduce the transmission and incidence of the disease. Accordingly, the aim of this study was to estimate the heritability for BL incidence and the genetic merit of sires for leukosis resistance in Holstein and Jersey cattle. Continuous scores and binary milk ELISA results for 13,217 Holstein cows from 114 dairy herds across 16 states and 642 Jersey cows from 8 dairy herds were considered. Data were obtained from commercial testing records at Antel BioSystems (Lansing, MI). Out of the 13,859 animals tested, 38% were found to be infected with the disease. Linear and threshold animal models were used to analyze the continuous and binary data, respectively. Results from both models were similar in terms of estimated breeding values and variance components in their respective scales. Estimates of heritability obtained with the 2 approaches were approximately 8% for both breeds, indicating a considerable genetic component underlying BL disease incidence. The correlation between the estimated breeding values from the 2 models was larger than 0.90, and the lists of top 10% bulls selected from each model had about 80% overlap for both breeds. In summary, results indicate that a simple linear model using the continuous ELISA scores as the response variable was a reasonable approach for the genetic analysis of BL incidence in cattle. In addition, the levels of heritability found indicate that genetic selection could also be used to decrease susceptibility to bovine leukosis virus infection in Holstein and Jersey cattle.

Further research is necessary to investigate the genetic correlations of BL with other production and reproduction traits, and to search for potential genomic regions harboring major genes affecting BL susceptibility.

Key words: bovine leukosis, heritability, milk ELISA, threshold model

INTRODUCTION

Bovine leukosis (BL) is a retroviral disease in cattle caused by the bovine leukosis virus (BLV). The disease causes a neoplastic condition of tissues that affects lymph nodes and lymphocytes, giving rise to clinical disease including bovine leukemia, lymphosarcoma, and malignant lymphoma. Bovine leukosis is a blood-borne disease, and the virus survives and transfers within lymphocytes (Ott et al., 2003); a small number of infected animals show clinical signs of the infection. The National Animal Health Monitoring System (NAHMS) reported that BLV was widely prevalent in US dairy herds and 89% of all operations had cattle seropositive for BLV (NAHMS, 1997). The report also indicated that 44% of dairy cattle in the United States were infected with BLV.

The virus can be transmitted in many different ways, including direct exposure to infected blood, saliva, semen, and milk. Kobayashi et al. (2010) studied 90 dairy farms in Japan and found that housing system, dehorning, and presence of horseflies were significantly associated with within-farm seroprevalence of BLV. However, infection rates are relatively low in utero and through ingestion of milk and colostrum from infected animals (Hopkins and DiGiacomo, 1997), although the virus may transfer from infected mothers to progeny during parturition (Nagy et al., 2007). The disease can also be spread by direct transfer of blood from one animal to another. Biting or sucking of insects may be a route of transmission, as well as several routine management practices and tools such as contaminated needles, dehorning, and ear taggers. Gouge dehorning, ear tagging, and branding can contaminate feed areas and other facilities with blood. Multiple use of the same

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needle during routine vaccinations, use of unsterilized needles, and failure to change gloves during pregnancy examination can also increase the number of BLV positive animals. In a self-contained naturally infected herd of 120 dairy cattle where reactors were not preferentially culled, the prevalence rate increased from 6.1 to 34.5% during 1976 to 1978 (Wilesmith et al., 1980). Bulls can also transmit the virus if semen contains blood or lymphocytes, and infection can occur also during natural copulation. Increasing animal density per pen increases the risk of infection (Kobayashi et al., 2010).

Bovine leukosis reduces milk production, increases death losses, and has a negative effect on the dairy cattle industry in general; BLV infection is one of many pathogens that also affect reproduction (Thurmond and Hietala, 1997; Moen et al., 1998; Bartels et al., 2006). Bovine leukosis is a disease that has important effects on the international animal industry and sale of animal products (Vanleeuwen et al., 2010). The estimated economic effect of BLV infection was \$44 million in the United States in 1987 (Thurmond, 1987), but the true cost of BLV infection may be greater than current estimates due to losses in milk production (Brenner et al., 1989; Wu et al., 1989). Decreased productivity and profitability is associated with the subclinical BLV infection (Erskine et al., 2012), and positive BL herds have been significantly associated with high infectious disease incidence, reproductive inefficiency, low milk production, and higher culling rates (Emanuelson et al., 1992). A BLV-negative cow has a longer life span, produces a total of 3.5% more milk, and has, on average, 48 fewer days open per lactation than a BLV-positive cow (Brenner et al., 1989). Advantages of negative over positive BLV animals were estimated at 488 kg of milk, 15 kg of milk fat, and 16 kg of milk protein per lactation (Byrem et al., 2011). Using data from 20 western states with large populations of dairy cows and 46.3% BLV prevalence, Ott et al. (2003) indicated that cows in test-positive BLV herds produced 218 kg (3%) less milk per year than cows in test-negative BLV herds. Similar estimates were reported by Emanuelson et al. (1992) with data from 14,424 herds in Sweden, in which the decline in milk production associated with BLV infection was 2.5%. Even when BLV infection does not seem to affect the overall animal health, it still affects significantly the milk yield (Motton, 2002).

Some other studies used individual cow data to investigate the association between milk yield and BLV infection, and different results have been reported. The difference between test-negative and test-positive BLV herds was 3.5% per cow per year (Brenner et al., 1989); however, this percentage was 11% according to D'Angelino et al. (1998). Nationally it was estimated that BLV reduced milk production by 0.7% in 1995 and

led to a loss of \$285 million for producers. Moreover, such a loss in milk production cost consumers an additional \$240 million in that year, bringing the total economic loss due to BLV infection up to \$525 million, without including any veterinary expenses associated with BLV (Ott et al., 2003). In another study, Thurmond (1987) estimated the nonmilk economic losses at \$80 million. In Michigan, reduced milk production was associated with increased BLV prevalence, and BLV affected economic status in high-producing dairy herds (Erskine et al., 2012). High disease incidence in dairy herds increases the expenses associated with milk production, and, because BL affects the immune response to some vaccinations (Yamamoto et al., 1984; Erskine et al., 2011), this might be the reason behind an association between BLV infection and incidence of other diseases.

Furthermore, restriction of exports is one of the most important economic effects of BL disease. Animals or animal products infected with BLV cannot be accepted in many countries, and large monetary losses may occur to breeders by rejecting heifers, embryos, or semen produced from their animals.

Bovine leukosis virus is not known to cause disease or even to be transmissible to humans. However, higher attention and concern was brought after discovery of the human T cell leukemia virus type 1 (HTLV-1) and the significant effect of retroviruses as human pathogens (Poesz et al., 1980); HTLV-1 is considered to be the cause of adult T-cell leukemia (Acheson, 2007; Matsuoaka and Jeang, 2007). The BLV and HTLV-1 genome sequences, as well as sequences of their proteins (amino acids), are similar enough to infer that both viruses have a common ancestor (Willems et al., 2000). In addition, some research has shown a potential link between consumption of BLV-contaminated dairy and beef and incidence of breast cancer worldwide (Rees, 2012).

Clinical signs of BL are rarely seen, and in most cases a clinical test is required to determine whether an animal is infected (Schwartz and Levy, 1994). Milk ELISA test is one of the methods used for that purpose; ELISA is an assay to detect the antibodies linked to BLV in milk or blood samples. The estimated sensitivity of milk ELISA is 98%, the specificity is 100% (Jacobsen et al., 1985; Monke et al., 1992). Results of the milk ELISA test are recorded on a continuous scale and then dichotomized using a threshold of 0.1; animals with milk ELISA score higher than that cutoff are considered infected.

Dairy studies published in 1997 and 2007 (NAHMS, 2007, 1997) reported similar percentages for the presence of antibodies against BLV, indicating ineffective progress in reducing the prevalence of the disease. However, taking into account that different testing methods

(AGID vs. milk ELISA) were used, it is expected that BLV prevalence has been increased considering that the ELISA test has higher sensitivity compared with the AGID test (Buzala and Dereñ, 2003). Due to the unfavorable genetic correlation between milk production and many undesired traits, including diseases (Pryce et al., 1997; Rauw et al., 1998; Sandoe et al., 1999), improvements in milk production per cow may be a factor contributing to increased incidence of BL. Bovine leukosis has received some attention in the veterinary and microbiology literature, but very few genetic studies have been performed. Bovine leukosis has not been included in the breeding objectives of US dairy cattle; one reason might be that the heritability for BL has been estimated to be zero, as reported by Detilleux et al. (1995). That estimate, however, was based on serum samples that were taken around time of calving from 124 cows only, and using a commercial kit (Leuk-Assay B; Pitman Moore Inc., Mundelein, IL) to determine BLV infection. At any rate, it has been shown that environment and management practices are important factors in disease transmission. Nevertheless, if a genetic component associated with the disease exists, it can be exploited to decrease the susceptibility of animals to BLV.

The NAHMS indicated that current management procedures were ineffective in reducing the prevalence of BL (NAHMS, 2007). At present, no vaccine is available to prevent transmission of BLV to uninfected animals, and no treatment or cure exists for those that are infected. For the reasons stated above, any possible genetic increase in resistance to the disease would assist in alleviating the detrimental effect caused by the infection on milk production. Therefore, the objectives of this study were to investigate the heritability of BL incidence and estimate breeding values of Holstein and Jersey sires for BL. In addition, the analyses were performed using both the milk ELISA scores and results (diagnoses) to assess their suitability and compare their (dis)advantages. The ELISA score, as a continuous variable, was analyzed using a linear Gaussian model

after log-transformation; the ELISA result (positive or negative), as a binary outcome, was analyzed using a threshold model.

MATERIALS AND METHODS

Data

Data were provided by the commercial diagnostic testing division of Antel BioSystems (Lansing, MI). Pedigree information and production records were obtained from the USDA-Agricultural Research Service Animal Improvement Programs Laboratory (Beltsville, MD). Data considered in this study included ELISA scores and ELISA results (positive or negative) for Holstein and Jersey cows. Animals were tested using 3 different milk samples and those samples were taken approximately 1 yr apart. Data used for analysis were limited to those animals that showed 3 ELISA scores with all either below or above the threshold and hence a total of 3 positive or negative results. Only herds with at least 10 cows were included in the study, so that the final data comprised ELISA scores for 13,217 US Holstein daughters of 2,679 sires in 114 herds across 16 states, and 642 US Jersey daughters of 284 sires from 8 herds (Table 1).

The final pedigree files included 41,321 and 1,832 animals for Holsteins and Jerseys, respectively. The data were recorded from 2004 to 2010, and age of cow at milk ELISA testing was between 23 and 119 mo. Because no apparent signs of the disease were observed in most cases, animals included in the study were chosen by random sampling such that both suspect and nonsuspect cows were tested. The range of milk ELISA score was -0.01 to 2.98 for Holsteins and -0.04 to 0.77 for Jerseys. Cows that had milk ELISA scores above 0.1 were considered as infected with the disease. Based on that cutoff point, 38% of the Holstein cows and 30% of the Jersey cows were positive for BLV. The milk ELISA test was evaluated against a serum ELISA test using samples drawn on the same day from 2 herds with a high prevalence of leukosis; the milk ELISA had

Table 1. Summary statistics of the data available after editing

Description	Holstein	Jersey
Records, no.	13,217	642
Sires, no.	2,679	284
Daughters per sire, mean no.	5.08	2.26
Pedigree, no.	36,931	1,832
Herds, no.	114	8
Birth year, range	1994–2008	1994–2008
Age at test, mo	23–119	23–119
Age groups	13	6
Milk ELISA score (range)	-0.101 – 2.98	-0.04 – 0.77
BL frequency, ¹ %	38	30

¹BL frequency = percentage of positive bovine leukosis virus cows. Cutoff point of (0.1) was used to obtain this percentage.

Figure 1. Box plot for Holstein ELISA scores before (a) and after (b) log-transformation. The dark line represents the median; the box around the median represents the upper and lower quartile. The dots above and below the quartiles represent outliers. The 2 horizontal lines represent the maximum and minimum values excluding outliers.

an overall agreement of 98.9% with the serum ELISA, and this value reached 100% when samples were drawn from suspect animals.

The observed ELISA score distribution was skewed to the right (Figures 1a and 2a). All analyses of ELISA scores, in its continuous scale, were then performed after a log-transformation to improve its normal approximation (Figures 2a and 2b).

Models of Analysis

The BL data available for this study included a preliminary continuous ELISA score that was measured

for each cow, which was then dichotomized to a binary scale based on an arbitrary cut-off. Therefore, we used both variables (ELISA scores and ELISA diagnoses) and compared the results obtained from 2 independent analyses, one based on a linear model (after suitable data transformation) and another based on a threshold model, respectively.

Both linear and threshold models have advantages and disadvantages. The linear model, generally used in the analysis of continuous traits, is based on the assumption of normality and is simple to implement using publicly available software. However, if the assumption of Gaussian distribution of the response variable is

Figure 2. Box plot for Jersey ELISA scores before (a) and after log-transformation (b). The dark line represents the median; the box around the median represents the upper and lower quartile. The dots above and below the quartiles represent outliers. The 2 horizontal lines represent the maximum and minimum values excluding outliers.

not met, for example due to skewness or the presence of outliers, results from a linear model analysis may be unreliable. Alternatives are the use of a data transformation or a more flexible modeling approach (Stranden and Gianola, 1999; Rosa et al., 2003). The threshold model, conversely, is specifically suitable for the analysis of binary traits. It is based on the assumption of a Gaussian distribution of unobservable liability values on an underlying scale. The analysis on the liability scale is similar to a Gaussian linear model, but a threshold model involves an extra step that links the expectation of the binary response variable to the linear predictor describing the fixed and random factors affecting the liabilities (Wright, 1934; Gianola, 1982; Gianola and Foulley, 1983). Such a link function, also called probit, is derived from the cumulative function of a Gaussian distribution.

In some applications, for example with calving traits, a sire-maternal grandsire has been reported as advantageous relative to an animal model in terms of genetic parameters estimation (Moreno et al., 1997; Eaglen et al., 2012). However, in our study, animal and sire-maternal grandsire models gave very similar results and so the animal model was used for all analyses.

The data from Holsteins and Jerseys were analyzed separately. In both models (i.e., linear and threshold), age of animal at test, year of birth, milk yield, and herd were considered as fixed effects, and additive genetic effects were considered as random variables. Some additional description of the models used and their implementation strategies are provided below.

Linear Animal Model for ELISA Score. Milk ELISA score, measured as a continuous variable, was analyzed using a linear mixed model presented in matrix notation as

$$\mathbf{y} = \mathbf{X}\boldsymbol{\beta} + \mathbf{Z}\mathbf{a} + \mathbf{e},$$

where $\mathbf{y}$ is a vector of observations of milk ELISA score; $\boldsymbol{\beta}$ is a vector with the fixed effects of herd (114 levels), age at test (13 classes for Holstein and 6 classes for Jersey), year of birth (1994 to 2008), and first lactation milk yield as a continuous covariate (regression); $\mathbf{a}$ is a vector of additive genetic effects (i.e., breeding values), distributed as $\mathbf{a} \sim N(0, \mathbf{A}\sigma_a^2)$, where $\mathbf{A}$ is the numerator relationship matrix; $\mathbf{e}$ is a vector of residual effects, distributed as $\mathbf{e} \sim N(0, \mathbf{I}\sigma_e^2)$; and $\mathbf{X}$ and $\mathbf{Z}$ are incidence matrices that link individual milk ELISA scores to their respective fixed and random effects.

Threshold Model for ELISA Results. A threshold-liability model was used to analyze the binary data (Wright, 1934; Gianola, 1982; Gianola and Foulley, 1983). The threshold model assumes an underlying

unobservable continuous random variable, liability (λ), and the observed binary response takes the value 1 if λ is greater than a fixed threshold (τ), and 0 otherwise. Liability is assumed to be normally distributed. The residual variance (σ_e^2) and the threshold value (τ) are not identifiable. Therefore, these parameters are set to arbitrary values (e.g., $\sigma_e^2 = 1$ and $\tau = 0$). The underlying liability to BL was analyzed using a linear predictor relative to an animal model, which can be represented in matrix notation as

$$\boldsymbol{\lambda} = \mathbf{X}\boldsymbol{\beta} + \mathbf{Z}\mathbf{a} + \mathbf{e},$$

where $\boldsymbol{\lambda}$ is a vector of unobserved liabilities of all cows, and the other effects are as for the linear model described above.

The REML and Bayesian Markov Chain Monte Carlo methods were used to estimate the variance components in the linear and the threshold models, respectively. Analyses were implemented using the programs AIREMLF90 and THRGIBBS1F90 (Misztal et al., 2002), respectively. Estimated variance components were used to obtain EBV using BLUPF90 (Misztal et al., 2002). The agreement between EBV obtained from both models was assessed through visual inspection of the scatter-plot, correlation coefficient, and overlap between lists of top 1, 5, 10, and 25% of the bulls for each model.

RESULTS AND DISCUSSION

Estimates of heritability for BL incidence in the Holstein population from the linear and threshold models were approximately 8%. The heritability estimate from the linear model was slightly higher (0.084 ± 0.013) than the estimate from the threshold model (0.081 ± 0.016). A similar heritability estimate was obtained using the Jersey data with the linear model, but with higher standard error (0.083 ± 0.074). However, a lower heritability estimate was found for the Jersey data with the threshold model (0.071 ± 0.059). The higher standard error from the linear model and the lower heritability estimate from the threshold model with Jersey data are probably due to its smaller sample size. A possible bias may also exist between large and small herds due to differences in management practices, which may potentially affect estimates of genetic parameters (Phocas and Laloë, 2003). No previous studies can be used to compare these results, with the exception of a single report (Detilleux et al., 1995), which used a sample size much smaller than the sample of Jerseys in this study. Moreover, the test used to detect BLV infection in that study and the samples taken were also different

to those used in the current study. In general, the assay used in the present study is known to provide more accurate results due to greater sensitivity and specificity.

Heritability for health traits is usually low, indicating that environment plays an important role in susceptibility to diseases. However, several studies have shown that current quantitative genetic approaches may not capture all of the genetic variance inherent in disease traits, which may contribute to the low heritability estimates (Bishop and Woolliams, 2010; Bishop et al., 2012; Lipschutz-Powell et al., 2012). Using simulated data, Lipschutz-Powell et al. (2012) found that conventional genetic models were not able to capture host genetic variation in infectivity, if present. However, indirect genetic effect models were able to capture some of that genetic variance. Many others factors may affect the estimate of disease resistance heritabilities, such as variation in exposure to the infection and disease and diagnoses tests (Bishop and Woolliams, 2010). As a result of such downward heritability estimates, potentially greater responses to selection can be obtained than those initially predicted.

The relationship between bulls' EBV obtained using ELISA scores (continuous variable) and results (binary outcome) is shown in Figure 3a. Although a linear relationship is observed between the 2 sets of estimates, some values are far from the bulk of the distribution. Ranked EBV from the 2 modeling approaches are presented in Figure 3b. By considering the number of daughters available for each sire, it is clear that sires with more daughters present higher agreement in rankings between the 2 models. Although the animal model procedure was considered as the method of choice in this study, the available data were also analyzed using a

sire model approach and no significant differences were found between results from the 2 models. Sample size available for analysis might be a reason for the differences in heritability estimates between the 2 modeling approaches with the Jersey data, which gave a slightly smaller estimate with the binary ELISA results. With larger sample size and more than 4 daughters per sire, it might be expected that the 2 modeling approaches would give relatively similar estimates of heritability and ranking of sires. Jersey sires with 2 daughters or more also showed high agreement between the ranked EBV from the 2 models (Figures 4 a and b). As indicated earlier, the Jersey data set was small and most of the sires had fewer than 5 daughters. Nevertheless, if we consider that, for example, only 15% of the top bulls would be selected as breeders, it could be argued that using linear or threshold models would lead to basically the same set of bulls (overlapping more than 80%).

For Holsteins, the overlap between the top 1% of sires from the 2 modeling approaches was 70%, and this percentage increased according to the proportion of selected sires (Table 2). This trend is not surprising, because by increasing the number of the selected animals the effect of a single sire will be relatively low if it was selected by one model or both models at the same time. In terms of ranking of sires, the analysis of the Jersey data resulted in higher agreement between models than for Holstein. The percentage of agreement was 67% for the top 1% of Jersey bulls, and it rose to 94% for the top 25%. The effect of the small data set available for Jersey might be the reason behind the larger increments observed in the agreement between the 2 models with increase proportion of selected sires.

Figure 3. Relationship between EBV (a) and their ranks (b) for Holstein sires from the analyses of ELISA scores (continuous trait) and ELISA results (binary trait). Solid and open circles represent sires with ≥ 5 and < 5 daughters, respectively.

Figure 4. Relationship between EBV (a) and their ranks (b) for Jersey sires from the analyses of ELISA scores (continuous trait) and ELISA results (binary trait). Solid and open circles represent sires with ≥ 2 and 1 single daughter, respectively.

Overall, the results suggest that ELISA scores can be a good option for the genetic analysis of the BL susceptibility, including estimation of variance components and breeding values. The advantages of a linear model over a threshold model, mainly because of its simplicity of implementation, may make it a preferred alternative.

CONCLUSIONS

For both Holsteins and Jerseys, heritability estimates for BL incidence were relatively low (i.e., around 8%) and similar between the 2 modeling approaches. Such levels of heritability should not be neglected, as they indicate the existence of an important genetic component affecting susceptibility to BL, which could be used to genetically improve BL resistance and avoid the negative consequence of BLV infection in the dairy industry. In the case of Jerseys, the relatively small sample size may have had an effect on the observed differences between the estimates of BL heritability using the 2 models. Overall, for both breeds, sires EBV obtained from the 2 modeling approaches showed reasonable agreement, particularly for sires with more daughters. Similar results were obtained also in terms of herita-

bility estimates, suggesting that the linear model may be a preferable alternative for the genetic study of BL incidence, given its simplicity, availability of software, and avoidance of dichotomization of ELISA scores based on an arbitrary cutoff. In addition, by analyzing BL ELISA scores with a linear model, the potential extreme case convergence problem that may be encountered with threshold models is avoided.

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Table 2. The proportion of agreement between the 2 modeling approaches (continuous and binary ELISA outcomes) for different percentages of selected sires for Holsteins and Jerseys

Breed, %	Top			
	1%	5%	10%	25%
Holstein	70	76	79	83
Jersey	67	78	82	94

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