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Genes of the Major Histocompatibility Complex in Cattle

Roger T. Stone and Noelle E. Muggli-Cockett¹

Introduction

The search for simple genetic traits that can be used as markers to predict variation in more complex genetic traits has been ongoing for several decades. For a given gene to be useful as a marker, it must have multiple forms, alleles, that are readily identifiable. Also, the frequency for the different alleles of the gene in a population must be such that most animals have two forms of the gene instead of one, otherwise statistical analysis is difficult. Only a few relationships between markers and production traits reported thus far have been utilized in production practices, presumably because of economic considerations. However, inexpensive tests to predict the genetic potential of individual breeding animals for multiple traits having strong genetic influence would likely gain acceptance and benefit the livestock industry. Initial studies in this area attempted to use blood types or blood protein variants as markers. These markers (proteins) had no apparent relationship to the variation in economic traits themselves, nor was there any knowledge of their proximity or linkage to other genes controlling economically important traits.

Recombinant DNA technology has made the idea of marker assisted selection more feasible because it is now possible to isolate and study target genes that are known to, or are likely to, impact important traits such as disease resistance, reproduction, or growth. Also, as a result this technology it is possible to identify short stretches of DNA that are inherited in many allelic forms and are distributed randomly over the entire genome. This new kind of marker will allow for the identification of additional target genes through mapping studies and may be useful as tags to follow the inheritance of alleles of target genes which have limited numbers of allelic forms. Important advances in the statistical analysis of this type of genetic data have been made recently. All things considered, there is reason to be optimistic that in the next few years genetic markers can be useful as tools in selection programs.

In the past few years, we have concentrated on a complex cluster of genes that are known to be involved in the immune response. These genes are the major histocompatibility complex (MHC) which are referred to as BoLA in cattle. The MHC genes produce two types of protein products. The class I proteins are present on the surface of most cells and function in the rejection of foreign cells such as transplants, tumors, or virus-infected cells. The class II proteins occur in cells of the immune system and are important in antibody formation. Antibody formation is initiated when specialized cells in the immune system take up foreign proteins, antigens, and cleave them into small fragments that are bound by the class II proteins. The binding of antigen fragments from vaccines or pathogens is a critical step in antibody formation which makes the class II genes good candidates to be markers for disease resistance or overall immunity. There are several class II genes and most of these genes have many variants, alleles. Experiments utilizing inbred strains of mice have shown that different class II alleles recognize different fragments of an antigen with differing efficiencies. Some alleles did not recognize any fragments of a rather large antigen which leads to a lack of antibody production. This result may

provide an experimental basis for individual variations in antibody production observed in laboratory and domestic animals. We have isolated and characterized some of these class II genes from cattle and have used parts of these genes as probes to follow the inheritance of their allelic forms. We have also analyzed the association of several alleles with growth traits and antibody titers to vaccines.

Procedure

Bovine class II MHC genes were isolated from a library made by placing DNA fragments representing all of the bovine genome into a suitable cloning vector and using corresponding human genes to identify clones containing the genes of interest. The DNA sequences were determined for parts of the genes and the identity of the genes confirmed by comparing the sequences to previously sequenced human genes.

Blood samples from straightbred Hereford and Angus cattle were used for DNA preparations. To determine the alleles for the MHC genes, DNA was digested with restriction enzymes and the digested fragments separated according to size by electrophoresis. The DNA fragments corresponding to the various class II genes were detected by reacting them with specific parts (probes) of the genes that had been isolated and made radioactive. The pattern of fragment sizes defined allelic forms of each gene. Statistical analysis was performed to determine whether any allele of MHC genes in these herds had an association with birth weight, weaning weight, or yearling weight. Antibody titers to BVD and BRSV were determined by Dr. Clayton Kelling (Department of Veterinary Science, University of Nebraska, Lincoln) in response to vaccination and analyzed for associations with MHC type.

Results

Three of the genes isolated corresponded to the human DRB group of genes. Sequence analysis and other types of analysis showed that only one of these genes was functional. This result suggested that any statistical analysis should be based on the alleles of this functional gene and not those of the two nonfunctional genes. A representative of another class II gene family, DQB, was isolated and shown to have several alleles in cattle. A fourth gene, DIB, was found to be considerably different from any previously isolated genes. Further analysis showed that this gene was present only in cattle and other members of the cattle (Bovidae) family. From our data and data from other laboratories, it appears that members of the cattle family have a unique second cluster of at least three class II genes located a considerable distance from the traditional tightly linked MHC class I, DR and DQ gene cluster. These genes may provide other laboratories with the genetic tools to trace the evolution of the cattle family and it provides another set of markers to analyze for associations with production traits that may be controlled by genes located on this region of bovine chromosome 23.

Statistically significant associations of MHC allelic types were obtained with weaning weight, adjusted 205-day weight, preweaning average daily gain, BVDV antibody titers 60 days after vaccination, and BRSV antibody titers 30 days of age and after weaning. These associations are encouraging, but have to be interpreted cautiously. Several associations with

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MHC type alleles have been published, but a portion of these have not been confirmed in further experiments. Typically, these experiments utilize a small number of sires and it is not uncommon to obtain an association in the offspring from only one sire in a study. This suggests that the genes controlling the traits of interest may be separated from the marker genes by a considerable distance, which means that arrangement of alleles for marker genes and those of the genes of interest are not the same across sires because of recombination. All of the growth traits mentioned above were associated only with alleles of DIB and not those of DRB or DQB, which are close together (Table 1). The alleles of DIB recombine with the DRB and DQB 20% of the time, i.e., DIB is separated by a distance of 20 units. It may be important that the association of DIB with growth parameters was observed in both Angus sires in this study. The possibility that DIB is closer to a gene(s) that influences growth than are DRB/DQB, merits further investigation.

Perhaps the most important finding during the course of these studies is that there are many more alleles of the class II MHC genes than initially supposed. Based on DNA sequence data from this and other laboratories there are at least 20 forms, alleles, of both DRB and DQB. This could explain some of the inconsistency in past analysis for associations, because not all of the alleles were being detected.

Future studies will need to account for all alleles and will need to concentrate on well defined populations containing a minimum number of alleles. Albeit, based on the number of studies showing associations of the MHC types with growth, reproduction, and immune traits, there is reason to believe that there are genes other than the MHC genes on chromosome 23 in cattle that influence economically important traits. Efforts to map this chromosome may lead to the location of these genes, or at least markers, close enough to these genes to be used in genetic and/or selection studies.

Table 1—Least squares means of weight traits associated with DIB alleles

Sire DIB allele	Weaning weight (lb)	205 d weight (lb)	Prewaning ADG (lb/day)
Angus 86-1			
Allele 1	310.2	423.5	1.69
Allele 2	322.5	442.2	1.76
Angus 86-2			
Allele 1	316.6	424.8	1.69
Allele 2	357.5	472.3	1.91