Putative quantitative trait locus affecting birth weight on bovine chromosome 2[1,2]

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ABSTRACT: A genome scan for chromosomal regions influencing birth weight was performed using 151 progeny of a single Hereford × composite bull and 170 microsatellite markers spanning 2.497 morgans on 29 bovine autosomes. A QTL was identified at the telomeric end of bovine chromosome 2 (maximum effect at 114 cM) accounting for approximately 2.8 kg of birth weight or 0.64 residual standard deviations (after adjustment for sex of calf, age of dam, and breed of dam). No significant effect on growth from birth to weaning was detected in this region. The presence of this QTL within a resource herd composed of breeds common to the Northern Great Plains provides an opportunity to initiate marker-assisted selection to reduce birth weight with minimal effect on postnatal growth. Thus, potentially the amount and degree of dystocia can be reduced and the economic loss associated with calving difficulty lessened without compromise of subsequent growth performance. In addition, this finding indicates that significant genetic variation for birth weight (and presumably other production-related traits) exists within herds composed of commercially adapted *Bos taurus* germplasm.

Key Words: Beef Cattle, Birth Weight, Dystocia, Genetic Markers, Quantitative Traits

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Introduction

Identifying genes affecting quantitative traits (QTL) of economic importance in agricultural species has the potential to significantly increase the rate of genetic improvement through the use of marker-assisted selection. Using marker-assisted selection also provides the opportunity to more efficiently break antagonistic genetic correlations among traits. For example, estimates of the genetic correlation between direct effects on birth weight and yearling weight are approximately 0.5 across all breeds (Koots et al., 1994) and 0.58 in Miles City Line 1 Hereford (MacNeil et al., 1998). This genetic antagonism among direct effects results in a situation wherein selection based on phenotypes or breeding values for greater yearling weight may also significantly increase birth weight, thus potentially increasing the incidence and severity of dystocia (calving difficulty). The converse is also true; selection for lower birth weight will likely reduce yearling weight. Identification of genes or genomic regions affecting birth weight and not yearling weight or, conversely, yearling weight and not birth weight, will provide powerful tools to manipulate pre- and postnatal growth rates to fit individual environments and operations.

Genomic maps composed primarily of microsatellite (dinucleotide repeat motif) markers have been assembled from numerous publications and provide sufficient coverage to screen genomes for the presence of segregating QTL. Fort Keogh Livestock and Range Research Laboratory (**LARRL**) established a three-generation resource population composed of 151 backcross calves with which to perform a genome-wide QTL scan. The objectives of this research were to identify genomic intervals that contain genes additively affecting birth weight in the resource population and then to determine effects of the regions containing significant QTL on subsequent growth.

Materials and Methods

Population. A three-generation double-backcross population composed of Line 1 Hereford and Compos-

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ite Gene Combination (**CGC**) germplasm was used in this study. Line 1 is an inbred line of Hereford cattle established in 1934 and selected for postweaning growth since its inception (MacNeil et al., 1992). Composite Gene Combination is a composite breed consisting of ½ Red Angus, ¼ Tarentaise, and ¼ Charolais (Newman et al., 1993a,b). An F_1 bull was produced by mating a Line 1 Hereford bull to a CGC cow. This bull (#94574) then sired 151 calves, 78 from CGC dams and 73 from Line 1 dams. Each calf was weighed within 24 h after birth and again at weaning, when the calves averaged approximately 180 d of age. Average daily gain from birth to weaning was calculated and multiplied by 180 to establish the preweaning gain phenotype.

Marker Selection and Genotyping. An initial panel of microsatellite markers (n = 365) was identified on the basis of relative position, fragment size (to facilitate multiplexing), and scoring ease from the genomics database at the USDA, ARS, U. S. Meat Animal Research Center (Kappes et al., 1997; USDA, 2000). Informative markers spanning the genome were identified by genotyping the F_1 bull and his sire and dam. Additional markers were identified and screened to fill gaps created by uninformative markers. All PCR reactions were performed as described by Bishop et al. (1994). Markers identified as heterozygous and spaced at approximately 20-cM intervals throughout the genome (n = 170) were used to genotype all calves and dams.

Statistical Analysis. Birth weight and 180-d preweaning gain were analyzed by least squares, using a model that included fixed effects for breed of dam, age of dam, sex of calf, and all possible interactions. Residuals were calculated as deviations of observations from their expectations, given the model. These residual values were the phenotypes for interval mapping of QTL.

Chromosomal linkage maps were produced using BUILD and ALL functions of CRIMAP (Green et al., 1990). Paternal contribution at marker loci was determined using the CHROMPIC function of CRIMAP. Alleles from the composite and Line 1 were assigned values of 0 and 1, respectively. When definitive assignment of the paternal allele was not possible, the paternal allele was coded as missing.

Interval mapping was by least squares according to the method of Knott et al. (1996) and allowed for the possibility of single and double crossover between marker loci. For each individual, the probability of having inherited the Line 1 allele from the F_1 sire was calculated every 2 cM conditional on its marker genotype at the nearest adjacent flanking markers. At each chromosomal position, the regression of phenotype on the conditional probability of having inherited the Line 1 allele from the F_1 sire was indicative of the additive genetic or QTL effect at that locus.

Nominal significance was established by permutation analysis (Churchill and Doerge, 1994; Lui, 1997). After establishing the QTL effect, the phenotypes were randomly assigned to marker genotypes. These shuffled data reflecting the null hypothesis of no relationship between phenotype and genotype were analyzed as described for estimating the QTL effect. For each chromosomal position, the resulting regression coefficient was saved. This process was repeated 2,000 times. Upon completing the analyses of all random permutations of the data, the resulting vector of regression coefficients at each chromosomal position was sorted from largest to smallest. The QTL effect at that locus was then positioned relative to elements of the vector of regression coefficients from analyses of the permutated data, and the probability of a more extreme regression coefficient occurring by chance at that locus was found. This procedure takes into account the particular characteristics of the experiment in arriving at nominal probability levels specific to each locus (Churchill and Doerge, 1994). Approximate genome-wide significance levels were established by applying the Bonferroni correction to the nominal probability levels as described in Knott et al. (1998).

Results

A Line 1 Hereford × CGC F_1 bull (#94574) and his sire and dam were screened for heterozygosity using 365 microsatellite markers. A small number of markers were not scored or produced ambiguous results when the parents were scored. Observed frequencies of heterozygosity were 38% (138/361), 57% (202/356), and 57% (207/365) for the Line 1 Hereford sire, CGC dam, and F_1 bull, respectively. The latter two observations are consistent with previously published heterozygosity levels of 59.5% among *Bos taurus* × *Bos taurus* crosses (Bishop et al., 1994). The reduction in heterozygosity observed in the Hereford sire is consistent his being inbred (F_x = 0.32) and with the general level of inbreeding in the Line 1 population (MacNeil et al., 1992).

The suite of informative markers used for the genome scan included 170 microsatellite markers spanning 2.497 morgans representing all 29 bovine autosomal chromosomes. Briefly, average number of markers per chromosome was 5.9, and the average interval between markers was 17.9 cM, with the largest gap being on the centromeric end of chromosome 6 (45.3 cM). Each chromosome contained at least four informative markers, with the exception of chromosome 28, for which only three informative markers were identified.

As expected, residual birth weight was normally distributed with a mean of 0, with a standard deviation of 4.4 kg. A region of the telomeric end of chromosome 2 produced a peak (genome-wide significance $P = 0.014$) between markers BM2113 and OarFCB11 (BM2113 – 12.4 cM – Max. QTL effect – 5.6 cM – OarFCB11), as shown in Figure 1. The observed effect was 2.8 kg and is equal to 14.5% of the residual variance or 64% of the residual standard deviation. The peak on the telomeric

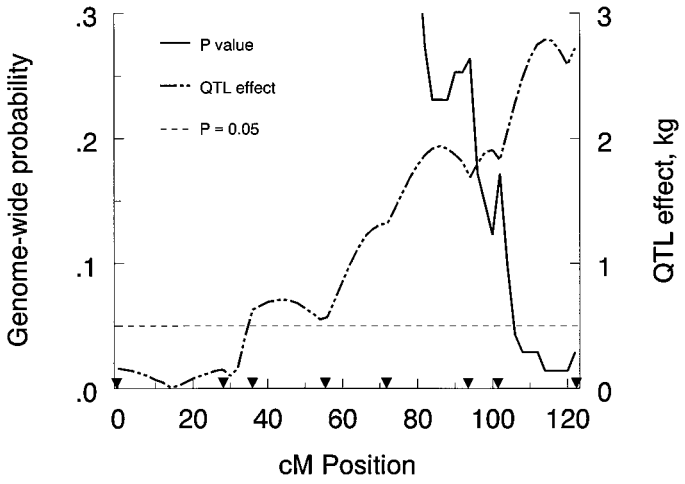

Figure 1. Plot of estimated size of birth weight QTL effect (kg: right y-axis) and genome-wide *P*-value (left y-axis) on chromosome 2 (cM position; x-axis). Marker positions are identified as triangles above the x-axis and were TGLA44, TGLA337, CSSM042, BMS1126, BMS1866, BMS1987, BM2113, and FCB11, respectively.

end of chromosome 2 was the only significant effect detected in this analysis. No significant effect of this region on preweaning gain was detected.

Discussion

A genome scan for chromosomal regions affecting birth weight was undertaken using 170 microsatellite markers spanning 2.497 morgans on 29 bovine autosomes. One peak on the telomeric end of chromosome 2 achieved genome-wide significance. The apparent "flattening" of the *P*-value around 108–122 cM is an artifact caused by 0.014 being the minimum obtainable genome-wide significance level using 2,000 permutations. No other chromosomal regions were shown to contain QTL effects on birth weight that reached genome-wide significance. The estimated allele substitution effect was approximately 2.8 kg, or 0.64 residual standard deviations (14.5% of residual variance), with calves receiving the Line 1 Hereford allele exhibiting lower birth weight. Although the objective of this research was to determine the average effect of substituting an allele from Line 1 for an allele from CGC, it is interesting to note the QTL effect was approximately 47% greater in the CGC backcross than in the Line 1 backcross. Thus, further investigation into potential nonadditive genetic effects may be warranted. Markers on chromosome 2 showed no significant effect on 180-d preweaning gain. This evidence indicates the presence of a gene at the telomeric end of chromosome 2 in the interval between BM2113 and OarFCB11 affecting birth weight, but not subsequent growth. There is confirming evidence for a QTL affecting birth weight in this location from the Texas A&M Angus-Brahman population (J. F. Taylor, personal communication).

Calf birth weight is the most significant single factor affecting dystocia (calving difficulty; Bellows et al., 1971; Meijering, 1984; Johnson et al., 1988). Dystocia affects many aspects of calf production, including death of calves and(or) cows, increased disease susceptibility, and lower calf weaning weights. In addition, dams surviving dystocia exhibit longer postpartum intervals, decreased milk production, and lower conception rates (Laster et al., 1973; Djemali et al., 1987; Colburn et al., 1997). Patterson et al. (1987) report that 45.7% of all preweaning deaths are due to dystocia. Annual deaths and veterinary costs due to dystocia have been estimated at $5,670 per 1,000 cows for dairy and $2,660 per 1,000 cows for beef cattle. Applying these cost figures to national herd numbers yields costs of $83.4 million (dairy) and $142.5 million (beef) annually due to dystocia alone (R. A. Bellows, personal communication).

Bellows et al. (1990) concluded that calf birth weight accounts for roughly 50% of the variation in dystocia. Also, Gregory et al. (1995) found a higher correlation between birth weight and calving difficulty score than between birth weight and yearling weight. Heritability estimates for birth weight range from 0.28 to 0.47 (MacNeil et al., 1998; Van Vleck and Cundiff, 1998). The strong positive genetic correlation (~0.5) between direct effects on birth weight and yearling weight (Koots et al., 1994) indicates that bulls selected for increased postnatal growth potential may be expected to also sire calves having greater birth weight, resulting in increased risk of dystocia. Similarly, breeders seeking to reduce dystocia through selection of sires with genetic potential to reduce birth weight have often concurrently sacrificed growth potential of the calves. Identifying genes affecting pre- and postnatal growth coupled with marker-assisted selection has potential to overcome this genetic antagonism by allowing selection for growth during specific developmental stages, thereby decreasing both the incidence of dystocia and economic loss inherent to calving difficulty while minimizing any coincident effect on postnatal growth. Further, maternal effects on calving difficulty may have a favorable genetic correlation with increased growth rate (MacNeil et al., 1984). Thus, selection on loci such as the one identified here, which affects birth weight but not subsequent growth, may be even more attractive because minimal effects on maternal calving difficulty would be anticipated.

The Fort Keogh QTL population was produced by backcrossing an F_1 bull (Line 1 Hereford × CGC) to Hereford and CGC dams. Because CGC is a composite herd derived from Red Angus, Charolais, and Tarentaise, the Fort Keogh QTL population contains germplasm from four breeds that are adapted and widely used in the Northern Great Plains. Thus, these data indicate the presence of functionally disparate alleles segregating between breeds that are believed to be less

diverse than those used in previous QTL identification studies. Some earlier QTL detection studies in beef cattle have used *Bos taurus* × *Bos indicus* crosses (Davis et al., 1998; Taylor et al., 1998; Stone et al., 1999). Such populations would be expected to contain significant genetic diversity, and therefore accommodate such experiments. However, animals of *Bos indicus* origin are not commonly used in the Northern Great Plains because of susceptibility to temperature stress. Other QTL identification studies have relied on crosses among *Bos taurus* breeds examining effects of the myostatin locus (e.g., Casas, 1998) and searching for QTL affecting ovulation rate and the frequency of twinning (Blattman et al., 1996; Kappes et al., 2000). However, these investigations also have not used germplasm that is commonly employed in commercial beef production in the Northern Great Plains. The presence of detectable segregation of alleles affecting birth weight among the *Bos taurus* breeds used in this research indicates significant variation affecting an economically important trait exists among breeds commonly used in commercial production on the Northern Great Plains.

Implications

Dystocia, associated with excessive birth weight, is a significant problem in both beef and dairy industries. Identifying genes affecting birth weight, but not growth at other developmental stages, will provide tools with which to break the genetic antagonism between birth weight and subsequent growth and more accurately describe the genetic merit of animals to be used for breeding. Coupled with marker-assisted selection (using molecular analyses to identify animals to be used for breeding), exploitation of loci such as has been presented in this paper can provide a mechanism to reduce birth weight and thus incidence and severity of dystocia without affecting postnatal growth.

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