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J Anim Sci 2007.85:341-347.
doi: 10.2527/jas.2006-460 originally published online Oct 13, 2006;

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http://jas.fass.org/cgi/content/full/85/2/341

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Association of a single nucleotide polymorphism in *SPP1* with growth traits and twinning in a cattle population selected for twinning rate[1,2]

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ABSTRACT: Continued validation of genetic markers for economically important traits is crucial to establishing marker-assisted selection as a tool in the cattle industry. The objective of the current study was to evaluate the association of a SNP (T_9/T_{10}) in the osteopontin gene (*SPP1*) with growth rate in a large cattle population spanning multiple generations and representing alleles from 12 founding breeds. This population has been maintained at the US Meat Animal Research Center since 1981 and subjected to selection for twinning rate. Phenotypic records for this population included twinning rate and ovulation rate, providing an opportunity to examine the potential effects of *SPP1* genotype on reproductive traits. A set of 2,701 animals was genotyped for the T_9/T_{10} polymorphism at *SPP1*. The genotypic data, including previously genotyped markers on chromosome 6 (BTA6), were used in conjunction with pedigree information to estimate genotypic probabilities for all 14,714 animals with phenotypic records. The genotypic probabilities for females were used to calculate independent variables for regressions of additive, dominance, and imprinting effects. Genotypic regressions were fit as fixed effects in a mixed model analysis, in which each trait was analyzed in a 2-trait model where single births were treated as a separate trait from twin births. The association of the *SPP1* marker with birth weight ($P < 0.006$), weaning weight ($P < 0.007$), and yearling weight ($P < 0.003$) was consistent with the previously reported effects of *SPP1* genotype on yearling weight. Our data supports the conclusion that the SNP successfully tracks functional alleles affecting growth in cattle. The previously undetected effect of the SNP on birth and weaning weight suggests this particular *SPP1* marker may explain a portion of the phenotypic variance explained by QTL for birth and HCW on BTA6.

Key words: genetic marker, marker-assisted selection, osteopontin, twinning

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J. Anim. Sci. 2007. 85:341–347
doi:10.2527/jas.2006-460

INTRODUCTION

Use of DNA markers to account for genetic variation for quantitative traits provides producers a tool to assist in genetic selection of superior animals. Whereas some marker-assisted selection is currently practiced in the beef cattle industry, a limited number of markers has been developed for use by cattle producers, and these markers explain a relatively small proportion of the genetic variation for a limited number of traits (Dekkers, 2004). Therefore, the need continues for more genetic markers associated with economically important traits.

Recently, Schnabel et al. (2005) proposed that a SNP upstream of osteopontin (***SPP1***) was a positional candidate polymorphism explaining a QTL on chromosome 6 that affected milk traits. White et al. (2007) was able to detect significant effects in 2 populations for post-weaning growth; birth weight and weaning weight, however, showed no significant associations. This lack of association was somewhat puzzling given the known biology of *SPP1* in terms of tissue growth (Rangaswami et al., 2006) and embryonic growth (Weintraub et al., 2004).

The US Meat Animal Research Center (**USMARC**) Twinning population has been selected for 25 yr on ovulation and twinning rate. Previous work has demonstrated that remarkable progress can be made by selec-

[1]Mention of trade names or commercial products in this publication is solely for the purpose of providing specific information and does not imply recommendation or endorsement by the USDA.

[2]The authors thank L. Flathman, K. Beavers, and D. Sypherd for technical assistance and D. Griess and J. Byrkit for secretarial support.

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Received July 11, 2006.
Accepted September 22, 2006.

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tion despite the low heritability of twinning rate (Gregory et al., 1997).

The objectives of this study were to evaluate the *SPP1* marker in the USMARC Twinning population, confirm *SPP1* as a marker for postweaning growth, evaluate the potential influence of *SPP1* on birth weight, and evaluate the genetic parameters between twin- and single-born animals for each growth trait. In addition, the Twinning population supported analysis of the effects of *SPP1* on reproductive phenotypes of twinning and ovulation rates. A subobjective of this study was to demonstrate the efficacy of detecting associations using a model with polygenic effects and genotypic probabilities.

MATERIALS AND METHODS

Animals and Phenotypes

These experimental procedures were approved by the USMARC Animal Care and Use Committee. The animals used in this experiment were from the USMARC Twinning selection experiment initiated in 1981 and described previously (Gregory et al., 1997). Briefly, the Twinning population was founded using 307 females and 53 males representing 12 breeds of cattle, including Angus, Brown Swiss, Charolais, Gelbvieh, Hereford, Holstein, Norwegian Red, Pinzgauer, Shorthorn, Simmental, Swedish Friesian, and Swedish Red and White. One-half of the cows have calved during the spring-calving season and one-half during the fall-calving season. The herd has undergone selection for increased twinning rate by direct selection on predicted breeding value for twinning and indirect selection on ovulation rate using repeated measurements of ovulation rate in 12- to 24-mo-old heifers (Echternkamp et al., 1990; Gregory et al., 1990; 1997).

Traits analyzed in the current study included birth weight (**BWT**), weaning weight adjusted to 205 d of age (**WW205**), yearling weight adjusted to 365 d of age (**YW365**), postweaning gain (**PWG**; weight gain between WW205 and YW365), twinning rate (**TWN**; number of calves per parturition), and ovulation rate (**OR**) as an indicator of the number of ova ovulated per estrous cycle as measured in heifers. Ovulation rate was determined by counting the number of corpora lutea by palpation or ultrasound or both in successive estrous cycles. Fostered animals, triplets, and quadruplets were removed from the data set.

Genotyping

The DNA extracted from ear notch or semen samples was genotyped for the *SPP1* polymorphism from 309 sires representing all of the males that had produced progeny, 116 males born in 2005 with available DNA, and 2,276 females born from 1988 to 2004. Additional nontwinner genotyping included the sire of the USMARC Belgian Blue × MARC III QTL population (Casas et al., 2000). This was done to evaluate the *SPP1* polymorphism in relation to previously discovered QTL for BWT and postweaning growth traits segregating in the region as a result of this sire.

Table 1. Map of bovine chromosome 6 used for GenoProb analysis of marker data

Marker name	Accession number[1]	cM[2]	No. of genotyped animals[3]
ILSTS093	BOVILS93	**0.0**	267
ILSTS090	BOVILS90	**15.36**	172
BM1329	G18422	**35.4**	292
BMS2508	G18959	**43.94**	184
SPP1	AY878328	53.0	2,701
BMS518	G18861	**58.97**	181
BMS470	G18569	**67.4**	299
BM4621	G18529	**77.61**	87
ILSTS035	BOVILS35	**87.26**	184
BMS2460	G19012	**93.45**	309
BM8124	G18801	**101.41**	174
BMC4203	G19110	**119.05**	292
BL1038	9107677*	**129.99**	183

[1]GenBank accession number available at http://www.ncbi.nlm.nih.gov, with the exception of the identification numbers followed by *, which is found in the publication given by the PubMed number.

[2]CentiMorgan (cM) positions in bold are microsatellite marker positions from the USDA, ARS, US Meat Animal Research Center linkage map.

[3]Number of animals with actual scored genotypes used for the GenoProb analysis.

The assay design for the *SPP1* polymorphism was previously described by White et al. (2007). Briefly, a polymorphism assay for a single base pair in length was developed to observe the alleles for the deletion/insertion polymorphism *SPP1*, previously described as OPN3907 (Schnabel et al., 2005). Alleles designated as T_9 and T_{10} describe 9 or 10 consecutive thymidine bases on the sense strand of *SPP1*, respectively. Microsatellite genotyping procedures were previously described by Kappes et al. (2000), and map positions were used directly from the USMARC linkage map (Snelling et al., 2005). Previously, Kappes et al. (2000) had genotyped 181 progeny-tested sires from this population for 12 microsatellites on BTA6. An additional 128 progeny-tested sires were genotyped for 5 of the 12 microsatellites (Table 1).

Analysis

The number of records used for the trait analyses is listed in Table 2. Genotype probabilities for all animals in the extended pedigree (n = 14,714) were calculated using an extended version of the GenoProb software (Thallman, 2002). The map used by GenoProb included 12 microsatellite markers and the *SPP1* SNP for bovine chromosome 6 (Table 1). The genotypic probabilities, calculated from GenoProb, were used to calculate independent variables for regressions of additive, dominance, and imprinting effects. The individual indepen-

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Table 2. Number of records used for growth and reproductive traits for all animals and females[1]

	All animals		Females	
Trait[2]	Single	Twin	Single	Twin
BWT	7,581	4,942	3,592	1,312
WW205	6,710	3,607	3,243	1,031
PWG	3,546	1,650	3,119	983
TWN	—		9,272	
OR	—		29,485	

[1]Females used to estimate the effects of *SPP1*.
[2]Traits: BWT = birth weight; WW205 = weaning weight adjusted to 205-d of age; PWG = postweaning gain; TWN = twinning rate; and OR = ovulation rate.

dent variables for animal j were obtained from the vector $\mathbf{x}_j$:

$$\mathbf{x}_j^{\mathrm{T}} = \begin{bmatrix} x_A \\ x_D \\ x_I \end{bmatrix}_j = \begin{bmatrix} 0 & 1 & 1 & 2 \\ 0 & 1 & 1 & 0 \\ 0 & 1 & -1 & 0 \end{bmatrix} \begin{bmatrix} P_{T10/T10} \\ P_{T10/T9} \\ P_{T9/T10} \\ P_{T9/T9} \end{bmatrix}_j,$$

where $p_{T10/T10}$ is the probability that j is homozygous for allele *T10*, $p_{T9/T9}$ is the probability that j is homozygous for allele *T9*, $p_{T10/T9}$ is the probability that j inherited allele *T10* from its dam and allele *T9* from its sire, and $p_{T9/T10}$ is the probability of the heterozygote with the opposite parental inheritance. The regressors are x_A, x_D, and x_I for the additive, dominance, and genomic imprinting components of gene action, respectively. Components that were not statistically significant were dropped from the model.

Twinning rate and OR were fit together in a 2-trait, repeated-records analysis, using MTDFREML (Boldman et al., 1995) and the model described by Van Vleck and Gregory (1996). The model for TWN included the fixed effects of year of parturition, season of parturition, age at parturition, and genotypic regressions of *SPP1*. The model for OR included fixed effects of birth-year season, age at ovulation, month of ovulation, and genotypic regressions of *SPP1*. Random effects for both traits included breeding value with full relationships accounted for and environmental variance common to the repeated records of the animal in addition to the residual. Covariances between breeding values of the 2 traits were included, as were covariances between the common environmental effects of the 2 traits, but the residual covariance was set to 0 because there was no correspondence between ovulation records and twinning (parturition) records. (Co)variances were estimated by allowing MTDFREML to iterate until a convergence criteria of 10^{-14} was obtained and until the iterations resulted in no change in the parameter estimates upon restarting.

Two-trait analyses of growth traits were conducted using MTDFREML, with records from single births as 1 trait and records from twin births as the second trait to estimate genetic parameters for each growth trait. Four 2-trait analyses were run for the following combinations: BWT single births (**BWT-S**) – BWT twin births (**BWT-T**), WW205 single births (**WW205-S**) – WW205 twin births (**WW205-T**), PWG single births (**PWG-S**) – PWG twin births (**PWG-T**), and YW365 single births (**YW365-S**) – YW365 twin births (**YW365-T**).

For each trait, the fixed effects included a contemporary group effect, age of dam as linear and quadratic covariates, and individual and maternal genotypic regressions of *SPP1*. Dams greater than 10 yr of age were treated as 10-yr-olds. For all twin traits, birth order was added as a fixed effect. For BWT, the contemporary group included year-season of birth, type of birth (single, twin), type of rearing (animal raised as single, twin, or artificially), and sex (bull, heifer, or freemartin). For WW205, the contemporary group definition included type of rearing in addition to the factors for BWT. For PWG and YW365, the contemporary group definition included whether males were castrated shortly after weaning or not, in addition to the factors for WW205. Breeding value was included as a random effect for all 3 traits, again with a covariance structure defined by the numerator relationship matrix. For BWT and WW205, maternal breeding value and maternal permanent environment effects were fit as random effects in the model. All covariances among direct and maternal breeding values of the 3 traits were included, as were the covariances between the permanent environmental effects of the 2 maternal traits and all residual covariances. Variance component estimates were obtained using the same criteria as above.

The males with *SPP1* genotypes represented a small and highly selected proportion of the population. Furthermore, there were no *SPP1* genotypes on freemartins. Because of the potential for selection to bias the results, only female growth phenotypes were allowed to contribute to the estimates of genetic regressions for *SPP1*. This was accomplished by setting the *SPP1* regressors to zero for all male and freemartin records; this was effective because sex class was part of the contemporary group definition. Prior analyses on female data had shown that the predicted genotypes yielded similar estimates to the genotyped animals while increasing the power to detect effects. Retaining the records on male and freemartin calves in the analysis substantially improved the estimation of variance components, breeding values, and maternal permanent environment effects.

RESULTS

The USMARC Twinning population has phenotypic records for multiple generations of animals, but a significant number of these do not have available tissue samples for DNA genotyping. Therefore, the first goal was to genotype ancestral animals in the pedigree to determine phase relationships between markers on BTA6 and predict genotypes for females including those

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Table 3. Results of association analyses for *SPP1,* including additive effects with SE

Trait[1]	Effect[2] (SE)	*P*-value
BWT-S	1.14 (0.41)	0.006
BWT-T	0.67 (0.65)	0.3
WW205-S	5.16 (1.92)	0.007
WW205-T	3.34 (3.23)	0.3
YW365-S	7.89 (2.65)	0.003
YW365-T	3.06 (4.57)	0.5
PWG-S	1.55 (1.39)	0.27
PWG-T	0.96 (2.49)	0.7
TWN	0.032 (0.03)	0.23
OR	–0.003 (0.02)	0.88

[1]Traits: BWT-S = birth weight single birth; BWT-T = birth weight twin birth; WW205-S = weaning weight 205 d single birth; WW205-T = weaning weight 205 d twin birth; YW365-S = yearling weight 365 d single birth; YW365-T = yearling weight 365 d twin; PWG-S = postweaning gain single birth; PWG-T = postweaning gain twin birth; TWN = twinning rate; and OR = ovulation rate.

[2]Allele substitution effect for the T_{10} allele relative to the T_9 allele, expressed as kilograms for BWT, WW205, YW365, PWG, calves per parturition for TWN, and number of ova per estrous cycle for OR.

for which DNA was not available for direct testing. The *SPP1* SNP represents a biallelic marker providing limited information for establishing phase in animals without genotypes. Phase was established using microsatellites and *SPP1* genotypes on BTA6 for all sires used in the population. Previously, *SPP1* was placed in close proximity in a bacterial artificial chromosome contig to BM143 on BTA6 (Cohen-Zinder et al., 2005). Using the position of BM143 from the USMARC linkage map (Snelling et al., 2005), *SPP1* falls intermediate between markers BMS2508 and BMS518 used in the current study.

The *SPP1* polymorphism was segregating in the USMARC Twinning population with a minor allele (T_9) frequency in founders of 5.4% from the GenoProb analysis. Of the 2,701 animals genotyped, the minor allele frequency was 5.2%, with only 6 T_9/T_9 animals identified. Only 2 allele sizes, T_9 and T_{10}, were observed segregating in this population. The minor allele can be traced back to founders of Angus, Hereford, Holstein, Norwegian Red and Simmental decent. The Belgian Blue × MARCIII sire was heterozygous for the *SPP1* polymorphism.

Significant additive associations of *SPP1* were detected for animals of single births for BWT-S, WW205-S, and YW365-S with effects of 1.14, 5.16, and 7.89 kg, respectively (Table 3). Two-trait TWN and OR analysis resulted in no statistically significant association with *SPP1* marker genotype. No significant effects were identified for dominance and imprinting or for maternal genotype of *SPP1* in this population. These effects were subsequently dropped from the analyses. Heritability estimates for BWT-S and BWT-T were 0.5 and 0.33, respectively (Table 4). Proportion of permanent environmental variance was 0.015 for BWT-S and 0.14 for BWT-T. Genetic correlations among single and twin births for all growth traits were high with a range of r_g = 0.86 to 0.96 (Table 5). Additionally, the genetic correlation between TWN and OR was high (r_g = 0.77).

DISCUSSION

Consistent with the results observed in Germplasm Evaluation Cycles VII and VIII (**GPE7**, **GPE8**), the USMARC Twinning population demonstrated a significant association of *SPP1* with YW365-S (White et al., 2007) with a similar magnitude of effect. Additionally, a significant association was observed for BWT-S and WW205-S with effects of 1.14 and 5.16 kg, respectively. The SE of *SPP1* estimates were substantially greater in twins than in singles because of the smaller number of records and perhaps because of differences in data structure. Consequently, none of the associations of *SPP1* with growth traits in twins were significant. However, the estimated effects on all growth traits were in the same direction in twins as in singles. They do support the hypotheses that *SPP1* affects BWT-S, WW205-S, and YW365-S beyond the *P*-values reported for these traits. The estimated effects of *SPP1* on growth traits on twins were numerically smaller than in singles. If they are truly smaller, it is likely due to a combination of scaling and competition for the same maternal environment in twins.

No significant association was detected for *SPP1* on PWG. The estimated effects suggest that most of the impact of *SPP1* is realized prior to weaning (which is a component of YW365). The lack of significance for BWT and WW205 in White et al. (2007) does not support this conjecture. However, there are 2 possible explanations for differences in results between these 2 studies. First, BWT and WW205 were analyzed using a model with maternal effects in this study. This model accounted for genetic and permanent environmental variation in both of these traits and thereby decreased the residual error and increased the power to detect genotypic differences. Second, the calves analyzed in White et al. (2007) may have had reduced nutrient availability relative to this population due to the milking potential in the Twinning herd. Therefore, the White et al. (2007) calves may not have expressed their full growth potential prior to weaning and likely grew more postweaning in compensation. The direction of the effect is still toward increased growth in PWG for T_{10}/T_{10} Twinning females.

Analysis of TWN and OR resulted in no significant association of *SPP1* with either trait. Frequency of the minor T_9 allele was lower in the USMARC Twinning population (5.2%) than was observed in GPE7 (13.1%) and GPE8 (13.5%). Estimates of genetic parameters for BWT, WW205, YW365, TWN, and OR were consistent with previously published analyses (Gregory et al., 1997). However, our current analyses were the first to divide each growth trait into 2 separate traits (single and twin births). In BWT, the permanent environmental variance, and in WW205, the maternal heritability, were estimated higher in twin data than for single birth

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Table 4. Estimates of genetic parameters for growth traits using a birth type classification of single and twin births

Trait[1]	h_d^{22}	h_m^2	$r_{d,m}$	c^2	σ_p^2
BWT-S	0.50	0.07	–0.03	0.015	218.22
BWT-T	0.33	0.09	–0.21	0.14	196.64
WW205-S	0.34	0.04	–0.26	0.06	4,236.58
WW205-T	0.35	0.09	–0.29	0.06	3,883.64
YW365-S	0.51	—	—	—	6,635.67
YW365-T	0.55	—	—	—	7,537.19
PWG-S	0.31	—	—	—	1,832.45
PWG-T	0.39	—	—	—	2,109.70
TWN	0.10	—	—	0.035	0.2181
OR	0.08	—	—	0.065	0.1310

[1]Traits: BWT-S = birth weight single birth; BWT-T = birth weight twin birth; WW205-S = weaning weight 205 d single birth; WW205-T = weaning weight 205 d twin birth; YW365-S = yearling weight 365 d single birth; YW365-T = yearling weight 365 d twin; PWG-S = postweaning gain single birth; PWG-T = postweaning gain twin birth; TWN = twinning rate; and OR = ovulation rate.

[2]Within trait for: h_d^2 = direct heritability; h_m^2 = maternal heritability; $r_{d,m}$ = correlation of direct and maternal; c^2 = proportion of permanent environmental variance; and σ_p^2 = overall phenotypic variance.

data. Uterine environment (e.g., capacity, placental nutrients) may be more important when rearing twins because of potential limitations thereby increasing the permanent environmental variance in twin BWT. The increase in WW205 may be explained by the large proportion of dairy influence in this herd (Gregory et al., 1997). Females rearing single calves might not have had the opportunity to express their genetic potential for milking ability. This is a result of 2 calves having a higher capacity to consume milk than 1. Thus, the maternal or permanent environmental variances may be underestimated for the single birth animals.

Twin data has traditionally been ignored in sire evaluation for growth traits. Differences in direct heritability estimates for singles and twins for BWT suggest that twin animals should not be included in analyses with limited numbers of twin births. Lack of differences between estimates of heritability for weaning and postweaning growth traits suggests that twins may be included in the analyses. However, inclusion of twin data in genetic evaluation programs is likely dependent on having enough twin records to estimate genetic parameters.

The association of the *SPP1* SNP in this region of BTA6 is consistent with previously discovered QTL for growth traits in beef cattle. Early studies reported QTL for BWT on BTA6 mapping directly to the region containing *SPP1* (Davis et al., 1998; Casas et al., 2000). The estimated phenotypic difference between T_{10} and T_9 alleles was 1.14 kg of BWT in this study, about one-half the size of the effect for BWT reported in each of the previously listed QTL scans. A possible explanation for the difference may be that the region of BTA6 contains more than 1 gene having an effect on BWT. This also is supported by a BWT QTL just proximal to OPN reported by Kneeland et al. (2004). Additional QTL for correlated traits, calving ease and stillbirth, have been found in dairy cattle analyses by Schrooten et al. (2000) and Kühn et al. (2003), respectively, in the same region. It is possible that the effects for BWT QTL from the genomic scans may be overestimated, a common problem in QTL analyses (Bogdan and Doerge, 2005). Another possibility is that the size of effects can vary because of different genetic backgrounds.

In addition to the BWT QTL, Casas et al. (2000) detected QTL associated with postnatal growth traits in-

Table 5. Genetic correlations between traits estimated using bivariate analyses

Trait 1[1]	Trait 2[1]	r_d^2	r_m	$r_{d1,m2}$	$r_{d2,m1}$	$r_{c1,c2}$
BWT-S	BWT-T	0.86	0.79	0.11	–0.17	0.35
WW205-S	WW205-T	0.88	0.98	–0.12	–0.48	0.45
YW365-S	YW365-T	0.87	—	—	—	—
PWG-S	PWG-T	0.96	—	—	—	—
TWN	OR	0.77	—	—	—	—

[1]Traits: BWT-S = birth weight single birth; BWT-T = birth weight twin birth; WW205-S = weaning weight 205-d single birth; WW205-T = weaning weight 205-d twin birth; YW365-S = yearling weight 365-d single birth; YW365-T = yearling weight 365-d twin; PWG-S = postweaning gain single birth; PWG-T = postweaning gain twin birth; TWN = twinning rate; and OR = ovulation rate.

[2]Between trait correlations of: r_d = direct; r_m = maternal; $r_{d1,m2}$ = direct trait 1 and maternal trait 2; $r_{d2,m1}$ = direct trait 2, maternal trait 1; and $r_{c1,c2}$ = permanent environmental trait 1, permanent environmental trait 2.

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cluding yearling weight, HCW, and longissimus muscle area in this region in a Belgian Blue × MARC III sired population at USMARC. The Belgian Blue × MARC III sire genotyped T_{10}/T_9 adding additional support for the *SPP1* indel as positional mutation candidate for growth. However, it should be noted that the *SPP1* marker may be only in linkage with the functional mutation(s) for the growth QTL in this region. Another possibility is the indel could be functional for milk traits and an additional mutation in or near *SPP1* may be segregating for growth in this animal used to create the QTL mapping family. Additional evidence for postweaning ADG QTL has been mapped to this chromosome in the M1 Beefbooster line and in Hanwoo (Korean cattle) populations (Kim et al., 2003; Kneeland et al., 2004). In the M1 Beefbooster line, preweaning QTL have been mapped proximal and distal to the region containing *SPP1* on BTA6.

Schnabel et al. (2005) first described *SPP1* as a positional candidate for milk production traits in a Holstein population resulting from a QTL scan of BTA6. Previous research had indicated a role for *SPP1* in mammary gland development and lactation in a tissue-specific transgenic antisense RNA mouse model (Nemir et al., 2000). Schnabel et al. (2005) were able to show that the *SPP1* indel polymorphism was in concordance with all the sires segregating the QTL. When *SPP1* genotype was included as a fixed effect in the QTL analysis, evidence for the QTL in that region was completely eliminated. The authors concluded that the indel polymorphism lies upstream of the promoter of *SPP1* in a region that has been shown to contain tissue-specific regulatory elements, making it a strong candidate as the functional mutation for milk traits.

Osteopontin (*SPP1*, *OPN*, and *Eta-1*) is a secreted glycoprotein that plays a role in many different mammalian biological functions. It has been shown to be involved in cell adhesion, tissue remodeling, inflammation, cell survival, embryo implantation, and maintenance of pregnancy (Denhardt et al., 2001; Johnson et al., 2003). The role of *SPP1* in growth pathways has been studied extensively in bone tissue growth and cancer progression (Standal et al., 2004; Rangaswami et al., 2006). More recently, *SPP1* has been shown to increase in a myoblast proliferation and differentiation in vitro model (Ishibashi et al., 2005). Additional evidence of altered growth has been shown in *SPP1* knockout mice by examining embryo size in utero at 3 stages of gestation using magnetic resonance microscopy. Homozygous knockout mice had smaller embryos at all 3 stages of gestation with no differences in litter size when compared with the controls (Weintraub et al., 2004). The known biology and function of *SPP1* makes it an excellent positional candidate. However, we agree that much more work to investigate the functional biology of *SPP1* polymorphism is needed to consider the mutation as the causative polymorphism (de Koning, 2006).

IMPLICATIONS

The present association with growth shown in the US Meat Animal Research Center Twinning population, along with results from GPE7 and GPE8 populations continues to support the *SPP1* indel as a probable functional mutation candidate. The additional evidence relating *SPP1* to growth only supports this claim. Selection for the T_{10}/T_{10} genotype in marker-assisted selection could be beneficial due to the size of the effect on growth. However, it should be noted that increasing the frequency of the T_{10} allele in a population will increase birth weight. Producers should evaluate the frequency of the *SPP1* alleles in their populations and decide if the benefits of increasing the T_{10} allele for growth outweigh the possible increased incidence of dystocia associated with increased birth weight. Because of the high frequency of the T_{10} allele in the US Meat Animal Research Center Twinning population, GPE7 and GPE8, genetic testing may be most beneficial for producers wanting to maximize WW205 and postweaning growth through sire selection.

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