Evaluation in beef cattle of six deoxyribonucleic acid markers developed for dairy traits reveals an osteopontin polymorphism associated with postweaning growth

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ABSTRACT: The objectives of this study were to 1) estimate the allelic frequencies in US beef cattle of 6 DNA markers reported to be associated with variation in dairy production traits; and 2) evaluate the association of these markers with beef production traits. Several genetic markers have been associated with milk yield or composition, including polymorphisms in secreted phosphoprotein 1 (*SPP1*; also called osteopontin), growth hormone receptor (*GHR*), casein S1 (*CSN1S1*), diacylglycerol O-acyltransferase 1 (*DGAT1*), peroxysome proliferator-activated receptor gamma coactivator-1alpha (*PPARGC1A*), and ATP-binding cassette subfamily G (white) member 2 (*ABCG2*). Allelic frequencies for these 6 markers, and their association with 21 phenotypes, were evaluated in 2 crossbred beef cattle populations that sample influential industry sires. Five of 6 markers were segregating in beef cattle populations; the exception was *ABCG2*. The *SPP1* marker was associated with yearling weight ($P = 0.025$), live weight at slaughter ($P = 0.016$), postweaning ADG ($P = 0.007$), and HCW ($P = 0.007$) in a large, multisire population representing the 7 most populous beef breeds in the United States. Postweaning growth trait associations were confirmed in an independent population of similar construction, including sires from tropically adapted breeds. The *SPP1* marker was associated with yearling weight ($P = 0.034$), live weight at slaughter ($P = 0.011$), and postweaning ADG ($P = 0.015$) and showed a trend toward association with HCW ($P = 0.083$) in this population. Whereas *DGAT1*, *GHR*, and *CSN1S1* polymorphisms showed association with some traits in individual populations, the lack of consistent predictive merit between populations indicates they may not be suited for beef cattle selection. No significant associations were observed for the *PPARGC1A* marker and any of 21 recorded traits, indicating this marker had no apparent value in selection for the beef cattle traits tested in these populations. The *SPP1* marker had consistent associations and effect sizes (10.5 to 11.5 kg of live weight at slaughter) in both populations, providing strong evidence for utility of the *SPP1* marker for postweaning growth in beef cattle.

Key words: cattle, growth, marker, osteopontin, quantitative trait loci, *SPP1*

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INTRODUCTION

Marker assisted selection has great potential to improve genetic progress in cattle breeding. In addition, DNA markers may have utility in guiding management decisions by providing an indication of the likely genetic merit for specific production endpoints. Markers in 6 genes have had associations reported with milk composition or yield in dairy cattle. These 6 genes are diacylglycerol O-acyltransferase 1 (***DGAT1***; Grisart et al., 2002), growth hormone receptor (***GHR***; Blott et al., 2003), casein S1 (***CSN1S1***; Prinzenberg et al., 2003), peroxysome proliferator-activated receptor gamma coactivator-1alpha (***PPARGC1A***; Weikard et al., 2005), ATP-binding cassette subfamily G (white) member 2 (***ABCG2***; Cohen-Zinder et al., 2005), and secreted phosphoprotein 1 (***SPP1***, also called osteopontin, or *OPN*; Schnabel et al., 2005).

Of these 6 genes, only the *DGAT1* marker has been tested for possible effects in fat-related beef traits, and none have been closely examined for potential effects on other production traits that may be coselected during

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application of these markers. Most polymorphisms in taurine cattle are not breed-specific, suggesting the markers may be segregating widely in beef populations. Further, the involvement of these genes in fundamental biological processes such as fat production and growth suggests the markers may have importance for dairy and beef traits.

Six published dairy markers were tested in this study for their association with 21 growth and carcass traits in 2 multisire, multibreed, crossbred, beef cattle populations. The first population included influential sires from breeds of taurine cattle, and the second sampled sires from tropically adapted breeds. By using 2 separate test populations that sample breeds of widely different genetic backgrounds, we also examined the stability of marker-trait associations in diverse populations. The results provided large, standardized datasets including many phenotypes in separate populations of taurine- and indicus-influenced crossbred beef cattle.

MATERIALS AND METHODS

Experimental procedures were approved and performed in accordance with US Meat Animal Research Center animal care guidelines and the Guide for the Care and Use of Agricultural Animals in Agricultural Research and Teaching (FASS, 1999).

Populations and Phenotypes

Three sets of cattle were examined in this study. The first 2 were large (>500 phenotyped cattle), crossbred populations that have phenotypic data on 21 growth and carcass traits. The third was a breed diversity panel used only to estimate allelic frequency and has no connected phenotypes.

The first population included 564 crossbred steers that were part of the Germplasm Evaluation Project cycle 7 (**GPE7**) at the US Meat Animal Research Center (**MARC**). This population, its management and the collection of phenotypic data have been previously described in detail (Wheeler et al., 2005a). Briefly, approximately equal numbers of sires were chosen from the 7 most populous beef breeds in the United States (by annual registration): Hereford, Angus, Red Angus, Simmental, Gelbvieh, Limousin, and Charolais. Sires were mated to cows that were Angus, Hereford, or MARCIII (composite of ¼ Hereford, ¼ Angus, ¼ Pinzgauer, and ¼ Red Poll) to produce approximately equal numbers of calves per sire. Growth and carcass data were collected on steer calves as described (Wheeler et al., 2005a). Traits measured in this study included birth weight, weaning weight, 365-d adjusted yearling weight, live weight at slaughter, HCW, preweaning ADG, postweaning ADG, retail product yield, fat yield, bone yield, percentage of carcasses grading choice, yield grade, marbling, backfat depth, estimated KPH percentage, ribeye area, dressing percent, and d 14 Warner-Bratzler shear force. Trained sensory panel scores were taken for flavor, juiciness, and tenderness.

The second population included 606 crossbred steers that were part of the Germplasm Evaluation Project cycle 8 (**GPE8**) at MARC. This population has also been described in detail (Wheeler et al., 2005b). Briefly, approximately equal numbers of sires were chosen from the following breeds: Beefmaster, Brangus, Bonsmara, Romosinuano, Hereford, and Angus. These sires were mated to cows that were Angus or MARCIII to produce approximately equal numbers of calves per sire. Whereas overall the sire breeds tested were different between GPE7 and GPE8, there were 2 sire breeds in common, and the base cow herd was the same for each. This structure facilitated comparison of traits and adjustment of between-breed EPD (Wheeler et al., 2005b), and as a consequence a proportion (17% of total sires) from the Angus and Hereford breeds and some (30%) of the same MARCIII and Hereford dams were used in creation of both populations. Growth and carcass data were collected on the steers as described (Wheeler et al., 2005b), thereby providing the phenotypes collected for GPE7.

The third set of cattle was a breed diversity panel comprising 92 cattle from 15 beef breeds and 4 Holstein dairy cattle. The panel has been previously described in detail (Heaton et al., 2001). This panel was used solely to determine the approximate allelic frequency in US beef cattle in general (not by breed). No phenotypic data were recorded or analyzed for these cattle.

Markers and Genotyping

The DNA was extracted from blood of steers for genotyping. New assays were developed for 4 of the published polymorphisms to facilitate genotyping on a MassArray system using matrix-assisted laser desorption/ionization time-of-flight mass spectrometry (Sequenom Inc., San Diego, CA). The 2-bp substitution responsible for a K232A amino acid substitution in *DGAT1* (Grisart et al., 2002) will hereafter be referred to simply as *DGAT1*, and the genotypes for individual cattle at the locus will be designated AA, AK, or KK for homozygous Ala, heterozygous, or homozygous Lys, respectively. An SNP in the *GHR* responsible for a F279Y amino acid substitution will hereafter be referred to as *GHR*, and the genotypes will be designated FF, FY, or YY. An SNP in the promoter region of *CSN1S1*; Prinzenberg et al., 2003) having alternative alleles cytidine (C) or guanosine (G), will hereafter be referred to as *CSN1S1*, and the genotypes will be designated CC, CG, or GG. An SNP in *PPARGC1A* previously published as marker c.1892+19T>C (Weikard et al., 2005), having alternative alleles thymidine (T) or cytidine (C), will hereafter be referred to as *PPARGC1A*, with genotypes CC, CT, or TT. Table 1 shows the oligonucleotides used in these assays. An SNP in *ABCG2* previously published as marker *ABCG2*(2), that predicts an amino acid substitution of Ser for Tyr at residue 581 of the protein, was assayed on the Sequenom system using the primers previously described (Cohen-

Table 1. Genotyping assay primers

Marker	Forward primer	Reverse primer	Probe
GHR	GTGGCTATCAAGTGAAATCATTGAC[1,2]	ACTGGGTTGATGAAACACTTCACTC[1,2]	GCTAGCAGTGACATTAT
CSN1S1	AACAATGCCATTCCATTTCC[1]	GGTGATGGCAGACTTTTGCT[1]	ATCAATGTTCTGTTCAGTTC
DGAT1	CTACCGGGACGTCAACCTC[1]	GGTTGTCGGGGTAGCTCA[1]	AGCTCCCCCGTTGGCC
PPARGC1A	ACTACTATGAGTCAGGCCAC[1]	TCTACTCGAGGGATAAGAGG[1]	GGTAATGATGCACGTTCGC
SPP1	CATCCATAATTTTCTTTCAAACACC[3]	TTTCTCTCAGGATATATAAAATTGGTT	NA[4]

[1]Amplification primers are shown minus the standard mass tag for matrix-assisted laser desorption/ionization time-of-flight assays.
[2]Amplification primers for *GHR* according to Blott et al. (2003).
[3]Forward primer shown minus the 5′ extension used in the product labeling reaction of the length polymorphism assay.
[4]Not applicable; the sequence length polymorphism was genotyped by sizing of the PCR product (length polymorphism assay), not by probe primer extension.

Zinder et al., 2005). This marker will be referred to simply as *ABCG2*, with genotypes YY, YS, or SS.

The polymorphism in *SPP1* termed OPN3907 (Schnabel et al., 2005) was an insertion/deletion unsuitable for genotyping by mass spectrometry of an extension assay and was instead assayed as a length polymorphism on a LI-COR 4200 DNA Analysis System (LI-COR Biosciences, Lincoln, NE). The observed alleles consisted of 9 or 10 consecutive thymidine base pairs on the sense strand and will be referred to as T_9 or T_{10}, with genotypes T_9/T_9, T_9/T_{10}, or T_{10}/T_{10}. The forward primer contained a 5′, 19-mer to facilitate the use of standard primers end-labeled with either of 2 infrared dyes (IRD700 or IRD 800). Both dyes were included in each PCR to provide dye controls. Primers used in this assay are shown in Table 1.

Statistical Analysis

Association testing was performed using the MIXED procedure (SAS Inst. Inc., Cary, NC). The models used to test all traits were age-adjusted models that included the trait of interest as the dependent variable for GPE7 and GPE8. Sire breed, dam breed, sire breed × dam breed interaction, birth year, slaughter group within year, and marker genotype were included in the model as fixed effects, and weaning age was included as a linear covariate. Sire was included in the model as a random effect nested within sire breed. To further test carcass composition traits on a weight-adjusted basis, similar mixed models were used, which included weaning weight instead of weaning age as a linear covariate. Reported *P*-values are nominal, without adjustment for multiple testing.

Population haplotype frequencies were estimated, and haplotypes of individual cattle were determined by PHASE v2 (Stephens et al., 2001; Stephens and Donnelly, 2003). Most likely haplotype combinations were used in subsequent analyses if assigned with a confidence of at least 95%. Genotypes composed of haplotypes were analyzed using the same mixed models as for individual marker analyses.

RESULTS

The previously reported *DGAT1* K232A polymorphism (Grisart et al., 2002; Winter et al., 2002) was segregating in both test populations, with the lysine (K) allele as the minor allele having 10.4% frequency in GPE7 and 23.4% frequency in GPE8 (Table 2). This *DGAT1* polymorphism was associated with KPH in the GPE7 population, where the AA genotype was associated with higher KPH on an age-adjusted and weight-adjusted basis (Table 3; Table 5 online supplement). However, these associations were not repeated in GPE8. No other traits examined showed significant association with *DGAT1* genotype in either group of cattle (data not shown).

The previously reported *GHR* F279Y polymorphism (Blott et al., 2003) was segregating with the F allele as the minor allele with 11.5% frequency in GPE7 and 10.4% frequency in GPE8 (Table 2). The FF homozygote class could not be estimated because there were too few individuals (Table 2). In GPE7, the YY genotype of *GHR* was associated with lower yield grade, higher retail product yield, lower fat yield, higher bone yield, larger ribeye area, and less tender sensory panel tenderness score than FY heterozygotes (Table 3; Table 5 online supplement). With the exception of yield grade, which was not significantly associated with *GHR* genotype

Table 2. Genotype frequencies in each population

Genotype	GPE7 Population	GPE8 Population
DGAT1 marker		
AA	443	341
AK	107	228
KK	4	25
GHR marker		
FF	14	9
FY	100	109
YY	442	491
CSN1S1 marker		
CC	4	4
CG	79	59
GG	468	550
PPARGC1A marker		
CC	371	420
CT	145	181
TT	8	13
SPP1 marker		
T_9/T_9	9	9
T_9/T_{10}	120	144
T_{10}/T_{10}	399	449

Table 3. Statistical significance (*P*-values) of marker-trait associations observed in only 1 of the 2 beef cattle populations

	GPE7 Population[1]		GPE8 Population[2]	
Item	Age-adjusted	Wt-adjusted	Age-adjusted	Wt-adjusted
DGAT1 marker				
KPH	0.035*	0.037*	0.88	0.81
GHR marker				
Yield grade	0.024*	0.076	0.29	0.27
Retail product yield	0.009**	0.018*	0.48	0.52
Fat yield	0.002**	0.007**	0.33	0.35
Bone yield	0.014*	0.029*	0.61	0.62
Ribeye area	0.022*	0.007**	0.30	0.48
Tenderness score[3]	0.040*	0.040*	0.44	0.43
CSN1S1 marker				
365-d yearling wt	0.017*	—	0.57	—
HCW	0.043*	—	0.65	—
Postweaning ADG[4]	0.010**	—	0.73	—
Retail product yield	0.001**	0.001**	0.51	0.65
Fat yield	0.003**	0.009**	0.20	0.28
Bone yield	0.89	0.93	0.049*	0.060
KPH	0.39	0.41	0.016*	0.021*
SPP1 marker				
Marbling	0.37	0.34	0.007**	0.009**
% Choice[5]	0.95	0.91	0.004**	0.005**
Dressing percent	0.21	0.39	0.026*	0.020*
KPH	0.79	0.70	0.034*	0.046*
Yield grade	0.82	0.67	0.045*	0.089

[1]GPE7 = Germplasm Evaluation Cycle 7 crossbred population, as described in Wheeler et al., 2005a.
[2]GPE8 = Germplasm Evaluation Cycle 8 crossbred population, as described in Wheeler et al., 2005b.
[3]Sensory panel tenderness score.
[4]Postweaning ADG.
[5]Percentage of carcasses grading choice.
*$P < 0.05$; **$P \leq 0.01$.

on a weight-adjusted basis, the other associations had generally similar *P*-values in a weight-adjusted analysis (Table 3). None of the other traits examined showed significant association with *GHR* genotype in GPE7 (data not shown). These associations with multiple traits in GPE7 were not repeated in GPE8 (Table 3). Further, there were no significant trait associations in the GPE8 cattle (data not shown).

The previously reported *CSN1S1* polymorphism in allele 4 (Prinzenberg et al., 2003) was segregating with the C allele as the minor allele with 7.9% frequency in GPE7 and 5.5% frequency in GPE8 (Table 2). The rare CC homozygote class could not be estimated because of too few individuals (4 in each population). In GPE7, CG heterozygotes at *CSN1S1* were associated with lower yearling weights, lower HCW, lower postweaning ADG, higher retail product yield, and lower fat yield (Table 3; Table 5 online supplement). As with *GHR*, *CSN1S1* associations observed in GPE7 were not replicated in GPE8 (Table 3). The heterozygous class was only associated with lower KPH and bone yield in GPE8 (Table 3; Table 5 online supplement).

The previously reported *PPARGC1A* polymorphism was segregating with the T allele as the minor allele in both populations. The T allele was present at 15.4% in GPE7 and 16.9% frequency in GPE8 (Table 2). The TT homozygotes were omitted from association analysis due to the small numbers in this class, and the *PPARGC1A* polymorphism was not significantly associated with any of the traits examined in either population (data not shown).

The previously reported polymorphism in *ABCG2* resulting in a Y581S amino acid substitution (Cohen-Zinder et al., 2005) was assayed in a cattle breed diversity panel (Heaton et al., 2001). Of the 95 cattle tested, all were homozygous for the A allele, even though a Holstein panel did confirm the presence of the minor allele in that breed (data not shown). Because this indicates the marker is not present or is at extremely low frequency in beef cattle, it was not tested for association in GPE7 or GPE8.

The previously reported OPN3907 polymorphism (Schnabel et al., 2005), referred to here as *SPP1*, was segregating in GPE7 and GPE8 with the T_9 allele as the minor allele in both populations. The T_9 allele was present at 13.1% in GPE7 and 13.5% in GPE8 (Table 2). The T_9/T_9 homozygote class was dropped from association analysis because there were too few cattle of this genotype (9 in each population). The *SPP1* genotype was associated with 4 measures of weight gain in GPE7, including yearling weight, live weight at slaughter, ADG, and HCW (Table 4). For each measure of weight gain, the T_{10}/T_{10} homozygotes showed heavier weights than the T_9/T_{10} heterozygotes. Among the half-bred

Table 4. *SPP1* genotype contrasts between the genotypes indicated for adjusted yearling weight (YWT), live weight at slaughter (LWT), postweaning ADG (ADG), and HCW, by population

	No. of steers	YWT,[1] kg	LWT, kg/d	ADG, kg	HCW, kg
Item					
GPE7[2]					
T_9/T_{10}	120	0	0	0	0
T_{10}/T_{10}	399	9.08	11.5	0.042	7.98 kg
P-value		0.025	0.016	0.0065	0.0068
GPE8[3]					
T_9/T_{10}	144	0	0	0	0
T_{10}/T_{10}	449	7.32	10.5	0.030	4.58
P-value		0.034	0.011	0.015	0.083

[1]365-d, adjusted yearling weight.
[2]GPE7 = Germplasm Evaluation Cycle 7 crossbred population, as described in Wheeler et al., 2005a.
[3]GPE8 = Germplasm Evaluation Cycle 8 crossbred population, as described in Wheeler et al., 2005b.

steers in GPE7, the offspring of Hereford sires had the highest frequency of the T_9 allele. All effects noted were still significant in GPE7 after dropping Hereford-sired calves from the analysis (data not shown). Similarly in GPE8, the T_{10}/T_{10} homozygotes were significantly associated with weight gain, including higher yearling weight, higher live weight at slaughter, and higher postweaning ADG, compared with the T_9/T_{10} heterozygotes (Table 4). Although the association did not reach significance, the T_{10}/T_{10} homozygotes also showed a trend toward association with higher HCW (Table 4). Interestingly, in GPE8 the T_{10}/T_{10} *SPP1* genotype was also associated with higher marbling, higher percent of carcasses grading choice, higher yield grade, more KPH, and lower dressing percent, though these associations were not observed in GPE7 (Table 3; Table 5 online supplement). As in GPE7, the half-bred offspring of Hereford sires had the highest frequency of the T_9 allele in GPE8. All effects noted were still significant in GPE8 after dropping Hereford-sired calves from the analysis (data not shown). Haplotypes including *SPP1* and *PPARGC1A* were associated with sensory panel tenderness score in GPE8 ($P = 0.020$), but this association was not repeated in GPE7.

DISCUSSION

Selection in dairy cattle in the past has emphasized milk yield. Recently this emphasis has shifted to components of milk, such as the percentage of fat or protein and even more subtle differences such as types of fat. In response, research has focused more on milk quality and genetic variation that affects related traits. The development of DNA markers with predictive merit for dairy production traits has potential to have a positive impact on milk production, and several major research efforts have used quantitative trait loci analyses and related studies to identify DNA sequence variation having apparent association with a variety of dairy traits. These efforts have resulted in development of DNA markers reported to have predictive merit, or to be the causative difference, for milk yield and composition traits. It is likely that despite the differences between milk fat and carcass fat deposits more germane to beef cattle production, some genetic variation could affect fat in both settings. It is therefore of interest to determine if specific marker systems developed for fat-related dairy traits may be useful for selection in beef cattle. In addition, the implementation of selection based on markers raises the possibility that unintended, potentially negative, correlated responses in other traits may occur, making testing of markers for such responses an important research area.

Several studies reporting DNA markers for milk components and yield have focused on regions of the genome previously shown to carry variation affecting the trait(s) in QTL studies. Others have relied on a candidate gene approach wherein genes with known roles in milk or fat production are tested for existing DNA sequence variation. Markers reported in this study have been generated in both ways. Each of the 6 dairy marker systems will be discussed separately. Four of the markers (*ABCG2*, *CSN1S1*, *SPP1*, *PPARGC1A*) lie on bovine chromosome 6, the others on chromosomes 14 (*DGAT1*) and 20 (*GHR*). Each marker was tested individually to determine if it might be broadly useful in many beef cattle production contexts. One of the weaknesses of many trait association studies seeking to develop such markers is the use of only 1 test population. This makes it difficult to determine if an observed association will have predictive value in other situations. Therefore, we examined 2 separate populations to provide confirmation of marker-trait associations. Both populations sample multiple sires (~20) from each of several widely used breeds and include a relatively large number of half-sib families. This population design provides a stringent test for marker-trait association by requiring that any marker showing positive association 1) must be segregating in multiple families and 2) must have consistent trait association in many of those families.

The 2 populations designed in this way differed mainly in the sire breeds used. The GPE7 included sires from the 7 most populous sire breeds in the United States according to annual registration (Hereford, Angus, Red Angus, Simmental, Gelbvieh, Limousin, and Charolais), and approximately half of the sires in each breed were within the top 50 in terms of registered offspring, providing a representation of current industry germplasm. The GPE8 included sires from several tropically adapted breeds (Beefmaster, Brangus, Bonsmara, and Romosinuano), as well as Hereford and Angus to provide links between the 2 populations. The variety of sire breeds included in GPE7 and GPE8 expands the breadth of genetic representation and increases confidence for any marker found to be associated consistently with economically important traits

in both. These 2 populations formed the basis of the evaluation of genetic markers developed to address dairy traits for effects in beef cattle.

DGAT1

The discovery that removal of the *DGAT1* gene in mice has a dramatic influence on production of murine milk (Smith et al., 2000) was the genesis of the development of the *DGAT1* marker system (Grisart et al., 2002; Winter et al., 2002). A polymorphism on bovine chromosome 14 in the *DGAT1* gene that results in a substitution of lysine (K) for alanine (A) has been proposed to be the causative variation underlying a significant increase in the percent fat in milk and decrease in milk yield (Winter et al., 2002; Grisart et al., 2004). The polymorphism has also been reported to be associated with marbling in German Holstein and Charolais cattle (Thaller et al., 2003) and subcutaneous fat thickness in a Wagyu-Limousin cross (Wu et al., 2005). Further, QTL have been found on BTA 14 for fat depth, yield grade, and marbling score, among other traits (MacNeil and Grosz, 2002; Casas et al., 2003; Mizoshita et al., 2004).

A previous survey of cattle breeds indicated that the K allele is the minor allele, with somewhat higher frequency in *Bos indicus* breeds (Kaupe et al., 2004). Allelic frequency in the GPE7 and GPE8 cattle was consistent with that study, ranging from 10 to 24% K allele, respectively (Table 2). The K allelic frequency was too low in GPE7 to produce sufficient numbers of KK genotype for meaningful analysis, and association was only observed with KPH for the remaining KA vs. AA genotype contrast (Table 3). Thaller et al. (2003) observed that the K allele increased intramuscular fat, but the association observed in GPE7 had the opposite phase, with the AA genotype associated with higher KPH. However, in the Thaller et al. (2003) study, the increased marbling effect was a contrast of KK genotype, which was too infrequent to support estimation of effects in GPE7. In GPE8, KK cattle were included in the analysis, but no significant effects were observed for the marker in this population. It should be noted, however, that the majority of K alleles in GPE8 were derived from the *Bos indicus*-influenced sires. Such cattle could have genetic background effects from linked polymorphisms, such as those tested by Kuhn et al. (2004), which mitigate the effects of the *DGAT1* K allele on body fat.

The populations used in this study were larger and had much broader breed representation than the limited sample of Charolais cattle examined by Thaller et al. (2003). It is possible that there is an effect of *DGAT1* genotype on intramuscular fat in some genetic backgrounds (breeds) but not present more widely. It is also possible that the effect observed by Thaller et al. (2003) is restricted to the semitendinosus muscle, which was not specifically tested in our samples. Still, the lack of consistent association in these broadly representative populations suggests that the *DGAT1* marker has limited utility in marker-assisted selection of beef cattle to increase marbling in a way recognized by current grading systems in the United States.

Growth Hormone Receptor

A polymorphism on bovine chromosome 20 in the growth hormone receptor (***GHR***) gene results in a F279Y substitution of phenylalanine (F) with tyrosine (Y), and is suggested to be a causative mutation affecting fat yield, milk yield, and related traits in dairy cattle (Blott et al., 2003). Anecdotal evidence has connected this polymorphism with mature animal size (Blott et al., 2003). Other polymorphisms in and around *GHR* also have been shown to be associated with various beef traits, including growth, body weight, serum IGF1 concentration, and drip loss (Hale et al., 2000; Ge et al., 2003; Curi et al., 2005; Di Stasio et al., 2005).

The F allele was the minor allele in both populations (around 10% in GPE7 and GPE8; Table 2), reflecting a considerably different frequency than observed in the Dutch Holstein population sampled by Blott et al. (2003) in which the F allele was the major allele, present at greater than 80% frequency. In GPE7, the YY genotype was associated with more growth of lean muscle and less fat production as reflected in higher retail product yield, larger ribeye area, lower yield grade, and lower fat yield compared with the FY genotype (Table 3; Table 5 online supplement). However, these associations failed to be replicated in GPE8, where there were no observed associations with any of the 21 traits in this study. It may be that a study with a larger sample of FF homozygotes would find consistent associations because this genotype class was too small for inclusion in both populations used here. There could be confounding genetic background effects in GPE8 that limit the apparent value of the marker, especially given the different breed compositions of the 2 populations. It may be that the GPE7 results are more important because the sire breeds are more representative of US beef cattle than the GPE8 sire breeds. Still, the lack of consistent association between populations indicates that applicability of this marker is limited, and additional research would be required to define circumstances of appropriate use.

CSN1S1

A polymorphism on bovine chromosome 6 in the *CSN1S1* gene adds a binding site for the transcription factor ABF1 in the promoter region and has been associated with milk protein effects in dairy cattle (Prinzenberg et al., 2003). Although it is difficult to imagine a direct effect of variation in *CSN1S1* expression on growth and carcass traits, there have been multiple QTL reported on BTA 6 that affect birth weight, postweaning ADG, and longissimus area (Boichard et al., 2003; Casas et al., 2003; Kneeland et al., 2004).

The C allele that adds an ABF1 binding site to the promoter of *CSN1S1* was the minor allele in GPE7 and GPE8 (Table 2), with slightly higher frequency than the 3.8% observed among cows of dairy and dual-use breeds (Prinzenberg et al., 2003). The GG genotype at *CSN1S1* was associated with higher yearling weights, HCW, and postweaning ADG in GPE7, compared with the CG genotype (Table 3; Table 5 online supplement). These growth gains for the GG genotype came at the cost of lower retail product yield, higher fat yield, and a trend toward higher yield grade. Overall in GPE7, the GG genotype was associated with better growth and a bigger carcass, but the CG genotype was associated with a higher percentage of the carcass in retail product and less in fat. The CC genotype was too rare for meaningful comparison.

Similar to the case for *GHR*, none of the significant associations were confirmed in GPE8, where GG homozygotes were only significantly associated with lower KPH and lower bone yield. As with *GHR*, it may be that a study with a larger sample of CC homozygotes would find consistent associations, and there could be limited circumstances under which it would be appropriate to use this *CSN1S1* marker for selection in beef cattle. However, the current data indicate that the marker does not have general predictive merit, and more research would be necessary to determine utility in target populations.

PPARGC1A, ABCG2, and SPP1

The remaining 3 markers, *ABCG2*, *PPARGC1A*, and *SPP1*, all lie close to one another on bovine chromosome 6. Each has been proposed as a marker for what is likely to be the same QTL associated with milk yield and fat content observed in several studies (Georges et al., 1995; Zhang et al., 1998; Wiener et al., 2000; Freyer et al., 2003). There also have been QTL for carcass traits detected on BTA 6, including traits such as birth weight, preweaning ADG, and postweaning ADG on feed (Kneeland et al., 2004), backfat depth (Li et al., 2004), and longissimus area (Casas et al., 2003). Because it is difficult a priori to determine which marker(s) might be most favorably matched to putative functional polymorphism(s), all 3 were tested for their predictive merit with respect to the 21 beef cattle traits recorded in GPE7 and GPE8.

The *PPARGC1A* gene was identified as a positional candidate for the QTL because its product has key functions in activation of nuclear hormone receptors and transcription factors regulating energy homeostasis and mediates expression of genes involved in adipogenesis (Puigserver and Spiegelman, 2003). Numerous polymorphisms have been identified in the bovine *PPARGC1A* gene, but only the marker described above (see Materials and Methods) showed consistent segregation with milk QTL alleles (Weikard et al., 2005). The marker was polymorphic in both GPE7 and GPE8, but the CC vs. CT genotype contrasts did not show association with any of the growth or carcass traits tested in either population. The TT genotype class was too small for reliable estimation in either population (Table 2), and it is possible that populations with sufficient TT homozygotes would show some association. Although the lack of association in our data indicates the marker does not have broad utility for selection of beef cattle traits, it also suggests that selection for dairy characteristics may not have undesirable consequences with respect to any of the production traits collected for GPE7 and GPE8.

The potential role of *ABCG2* in milk production and quality is not clear, although the protein has been shown to affect secretion of certain substances (e.g., toxins) into milk (Jonker et al., 2005) and is upregulated in lactating bovine mammary gland (Cohen-Zinder et al., 2005). Despite this lack of definitive biological context, a polymorphism in the *ABCG2* gene has been proposed as the causative variation underlying the milk QTL (Cohen-Zinder et al., 2005). Preliminary testing of the *ABCG2* assay in a small panel of GPE7 sires indicated that the marker was not segregating in the population (data not shown), and the uninformativity of the marker in US beef cattle was supported by testing a multibreed panel (Heaton et al., 2001) in which all 95 cattle presented the YY genotype. In addition to preventing association analysis, this result indicates that this polymorphism has no apparent utility for marker-assisted selection in US beef cattle. This marker segregates at much higher frequency in Holsteins (Cohen-Zinder et al., 2005) than in any other breeds tested.

The third positional candidate gene examined for the bovine chromosome 6 QTL was the *SPP1* gene, also known as osteopontin (***OPN***). Mice with reduced expression of this gene experience multiple defects in mammary gland structure and milk component synthesis (Nemir et al., 2000; D'Cruz et al., 2002). An SNP in what is believed to be a regulatory region of the *SPP1* gene has been proposed as a causative mutation affecting milk yield, fat yield, fat percent, and protein percent in dairy cattle (Schnabel et al., 2005). In that study, the T_{10} allele decreased milk yield while increasing fat yield, fat percent, and protein percent, relative to the alternative T_9 allele. In contrast to the *ABCG2* marker, the 2 alleles of the *SPP1* marker were present in GPE7 and GPE8 with appreciable minor allelic frequencies (Table 2), supporting analysis of association. However, no associations with fat-related carcass traits were observed consistently in both beef cattle populations, indicating that this marker would have restricted use in selection of beef cattle with respect to marbling or other fat-related characteristics.

Consistent association of *SPP1* genotype with postweaning growth measures was observed in GPE7 and GPE8 (Table 4). Although no significant difference between genotypes was observed at weaning, there were large, significant differences between genotypic classes for yearling weight in GPE7 and GPE8. Effects on live

weight at slaughter were even larger and more significant than those on yearling weight in both populations. As predicted by these observations, *SPP1* genotype also was associated with postweaning ADG in GPE7 and in GPE8. The weight differences carried over into HCW with highly significant association in GPE7 and a trend toward association in GPE8. The consistent association in populations with very different breed compositions demonstrates the broad applicability of this marker for postweaning growth. Indeed, *SPP1* may mark underlying variation for the postweaning ADG QTL on BTA6 reported by Kneeland et al. (2004) that is less than 20 cM away on the Ihara et al. (2004) map, and to the more distal QTL on BTA6 for longissimus area, birth weight, yearling weight, and HCW reported by Casas et al. (2000).

There were no other observed associations between *SPP1* genotype and any recorded traits in GPE7. The weight differences between genotypes did not result in detectable differences in carcass composition. Further, the lack of associations with other measured traits suggests that selection for the favorable T_{10}/T_{10} homozygotes may not result in adverse correlated effects in any of the traits measured for this study. Because GPE7 was designed to be representative of the US beef population, it is reasonable to expect that these results would be typical of effects of applying the marker for selection of US commercial beef cattle.

In contrast to GPE7, GPE8 showed associations between *SPP1* genotype and additional traits. Some of the additional associations add to the benefit of selecting for the high growth T_{10} allele. The T_{10}/T_{10} homozygote class was associated with higher marbling and higher percent of carcasses grading choice in GPE8 (Table 3; Table 5 online supplement). However, other results indicate tradeoffs of selection on *SPP1* in this population. The T_{10}/T_{10} genotype was associated with higher yield grade, lower dressing percent, and higher KPH in GPE8. Because these associations were only observed in GPE8, it is not clear that use of the marker would improve nongrowth-related traits in most US beef cattle. Still, the consistently observed effect on postweaning growth and the favorable effects of the T_{10}/T_{10} genotype on marbling and percent of carcasses grading choice in the GPE8 population demonstrate the potential for added value from use of the *SPP1* marker.

One area for further study will be whether allelic frequencies of *SPP1* differ between breeds. It is not appropriate to estimate allelic frequencies within breeds from the genotypes of half-bred calves, and purebred sire genotypes were not collected. Therefore, our data cannot directly address this issue. However, the observed associations did account for breed effects in multiple ways. The model used to analyze both populations did include sire and dam breed effects. Further, in each population the frequency of the lower growth T_9 allele was determined by sire breed for the half-bred steers, and the sire breed with the highest minor allelic frequency was dropped for each population to address the possibility that a single sire breed could have an undue influence on observed effects simply due to frequency differences (data not shown). In each population, the Hereford-sired calves had a slightly higher T_9 allelic frequency than the other sire breeds, but dropping these Hereford-sired calves from the analysis did not eliminate significance for any reported trait association in either population (data not shown). This indicates that the observed associations did not arise from large effects in 1 breed overshadowing less important associations in the rest of the population. It should also be noted that bulls with high postweaning growth EPD, but undesirable *SPP1* genotypes may have special value in breeding programs because they have high genetic merit for growth at many other important loci (Gibson, 1994).

The growth effects in both populations and fat effects in GPE8 suggest a role of *SPP1* in energy balance, although previous studies of the gene in mice have not revealed specific roles in growth and mice lacking the gene entirely are of normal size and are fertile (Liaw et al., 1998). It is therefore possible that even if the *SPP1* marker is indeed responsible for mediating the milk QTL, the growth effect observed here may be acting through a linked functional polymorphism in a nearby gene. It would be of interest to see if the observed growth effects are related to feed efficiency, appetite, or some combination of both. These effects may also vary depending on environmental factors such as type of feed. The GPE populations are sent to the feedlot at weaning, so some of these results may not apply directly to calves grown on grass. The GPE calves also were slaughtered at less than 500 d, so our observations do not include mature cattle. Still, the fact that the significance and size of the *SPP1* growth effect increase with age shows that the underlying genetic variation is important for older calves.

Overall, *SPP1* showed a large, consistently observed effect on postweaning growth in a variety of populations. This is particularly noteworthy given that the genotypic effect measured was the difference between the heterozygote and one homozygote. Thus, the presence or absence of a single T_9 allele resulted in the differences observed in these 2 populations. Because the *SPP1* and *PPARGC1A* genes appear to lie relatively close to one another on bovine chromosome 6 (approximately 6 Mb apart in the draft genome sequence), haplotypes of the 2 markers were analyzed but no associations were observed consistently in both populations. Thus, addition of marker data from loci in potential linkage disequilibrium did not improve predictive merit of the *SPP1* marker.

This study examined 6 dairy genetic markers for segregation and predictive value in 2 crossbred beef populations. All but the *ABCG2* marker were segregating in US beef cattle. The *SPP1* polymorphism was consistently associated with effects on postweaning growth traits in both populations. Additional trait associations for this marker were observed only in 1 of the 2 popula-

tions, limiting support for use of the marker to select for other traits. The *DGAT1*, *GHR*, and *CSN1S1* markers did not have consistent association with any traits between the 2 populations, suggesting that these markers do not have broad utility for selection of any of the economically important traits tested in this study. Additional studies may establish certain restricted situations under which these markers can effectively guide selection. The *PPARGC1A* marker did not show significant associations with any of the traits tested and does not appear to have predictive merit for selection of major yield and quality traits in US beef cattle. However, if this marker is later found to be useful for other traits, the data presented here suggest that deleterious side effects of selection on the 21 traits examined are unlikely. Taken as a whole, these data highlight the importance of the use of multiple populations to validate genetic markers.

IMPLICATIONS

A genetic marker in the *SPP1* (osteopontin) gene has been published previously for selection of dairy cattle for milk yield, fat yield, fat percent, and protein percent. This study demonstrates the association of this *SPP1* gene marker with postweaning growth in beef cattle. Under the conditions of this study, cattle with 2 copies of the T_{10} allele weighed 10.5 to 11.5 kilograms (23.1 to 25.4 pounds) more at slaughter than cattle with only one copy of the T_{10} allele. This was true in 2 populations with very different genetic backgrounds, so this genetic marker should be useful for postweaning growth in beef cattle of many breeds. However, more studies will be necessary to determine the optimal feeding and growth conditions to best utilize cattle with this desirable genetic composition.

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