A comprehensive search for quantitative trait loci affecting growth and carcass composition of cattle segregating alternative forms of the myostatin gene[1,2]

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ABSTRACT: The objective of this study was to identify quantitative trait loci for economically important traits in two families segregating an inactive copy of the myostatin gene. Two half-sib families were developed from a Belgian Blue × MARC III (n = 246) and a Piedmontese × Angus (n = 209) sire. Traits analyzed were birth, weaning, and yearling weight (kg); preweaning average daily gain (kg/d); postweaning average daily gain (kg/d); hot carcass weight (kg); fat depth (cm); marbling score; longissimus muscle area (cm^2); estimated kidney, pelvic, and heart fat (%); USDA yield grade; retail product yield (%); fat yield (%); and wholesale rib-fat yield (%). Meat tenderness was measured as Warner-Bratzler shear force at 3 and 14 d postmortem. The effect of the myostatin gene was removed using phase information from six microsatellite markers flanking the locus. Interactions of the myostatin gene with other loci throughout the genome were also evaluated. The objective was to use markers in each family, scanning the genome approximately every 25 to 30 centimorgans (cM) on 18 autosomal chromosomes, excluding 11 autosomal chromosomes previously analyzed. A total of 89 markers, informative in both families, were used to identify genomic regions potentially associated with each trait. In the family of Belgian Blue inheritance, a significant QTL (expected number of false-positives = 0.025) was identified for marbling score on chromosome 3. Suggestive QTL for the same family (expected number of false-positives = 0.5) were identified for retail product yield on chromosome 3, for hot carcass weight and postweaning average daily gain on chromosome 4, for fat depth and marbling score on chromosome 8, for 14-d Warner-Bratzler shear force on chromosome 9, and for marbling score on chromosome 10. Evidence suggesting the presence of an interaction for 3-d Warner-Bratzler shear force between the myostatin gene and a QTL on chromosome 4 was detected. In the family of Piedmontese and Angus inheritance, evidence indicates the presence of an interaction for fat depth between the myostatin gene and chromosome 8, in a similar position where the evidence suggests the presence of a QTL for fat depth in the family with Belgian Blue inheritance. Regions identified underlying QTL need to be assessed in other populations. Although the myostatin gene has a considerable effect, other loci with more subtle effects are involved in the expression of the phenotype.

Key Words: Beef, Double Muscling, Genetic Markers, Loci, Myostatin Gene, Quantitative Traits

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Introduction

The development of polymorphic markers and linkage maps in bovine has made possible the identification of genomic regions where loci influencing economically important traits reside (Kappes et al., 1997). This will improve the potential to realize genetic progress, especially for traits difficult and(or) expensive to measure. Among the traits for which this technology would be most beneficial are carcass composition and meat quality.

In previous efforts, the effect of the myostatin gene and other quantitative trait loci (QTL) have been assessed on growth, carcass composition, and meat quality traits (Casas et al., 1998, 2000). Initially, the use of marker information in these families provided the data required to refine the position of the myostatin gene to bovine chromosome 2 and to establish its effect on economically important traits (Casas et al., 1998). In a further study, by using selective genotyping, the entire genome was evaluated. Regions where evidence suggested the presence of QTL were investigated by typing all available progeny and additional markers. Evidence

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supported the presence of loci influencing carcass composition and meat quality traits on six chromosomes (Casas et al., 2000). The objective of the present study was to detect loci with moderate effects located in unevaluated regions using the entire population. This report, in conjunction with Casas et al. (2000), presents a complete scan in all available progeny in families segregating an inactive myostatin allele.

Materials and Methods

Animals

Families used in this study have been previously described (Casas et al., 1998). Briefly, two half-sib families were developed using a Belgian Blue × MARC III (¼ Angus, ¼ Hereford, ¼ Red Poll, ¼ Pinzgauer) sire and a Piedmontese × Angus sire. Both sires were heterozygous for the myostatin gene (one active and one inactive allele), and approximately half of the progeny inherited one copy of the inactive allele and the other half inherited an active copy. Two hundred and forty-six ¼-Belgian Blue and 209 ¼-Piedmontese offspring were produced by matings primarily to MARC III dams.

Traits Analyzed

Offspring of the two sires were evaluated for growth and carcass traits. Birth (kg), weaning (kg), and yearling weight (kg) were recorded. Yearling weight was adjusted for age. Pre- and postweaning average daily gain were calculated based on the previous weights. Slaughter data were obtained at a commercial facility, and the wholesale rib was retrieved from the right side of each carcass for dissection into fat, muscle, and bone. The carcass traits evaluated were hot carcass weight (kg); fat depth (cm); marbling score; longissimus muscle area (cm^2); estimated kidney, pelvic, and heart fat (%); and USDA yield grade. Carcass traits predicted from rib dissection were retail product yield (%), fat yield (%), and wholesale rib-fat yield (%) (Shackelford et al., 1995). Meat tenderness was measured as Warner-Bratzler shear force (kg) at 3 and 14 d postmortem. To measure Warner-Bratzler shear force, steaks were thawed, cooked, and sheared as described by Wheeler et al. (1998) with the following exception. The preheating platen on the belt grill was set at 149°C, rather than disconnected. This change required that cooking time be reduced to 5.5 min from 5.7 min. Means and standard errors for the traits have been reported earlier (Casas et al., 1998).

Genomic Screen

The development of the bovine genetic map at the U.S. Meat Animal Research Center (Kappes et al., 1997; http://www.marc.usda.gov) and at other laboratories (Barendse et al., 1997) has resulted in the availability of genetic markers throughout the genome. Eighty-nine markers were used to search 18 chromosomes in each family at intervals of 25 to 30 cM. Regions on chromosomes 2, 5, 6, 7, 13, 14, 17, 19, 22, 27, and 29 were previously analyzed (Casas et al., 1998; 2000) and associated results are excluded from this report. Informative markers in the sires were chosen based on their location in each chromosome and ease of scoring. Amplification reactions for each marker were done with purified DNA extracted from blood with a saturated salt procedure (Miller et al., 1988). Amplification conditions have been described elsewhere (Kappes et al., 1997).

Statistical Analysis

An *F*-statistic profile was generated at 1-cM intervals for each genomic region. Data were analyzed using the approach suggested by Haley et al. (1994), with a model that included the effects of sex, dam line, and days on feed and the conditional probability of inheriting the inactive myostatin allele from the sire as covariates. The conditional probability of inheriting the Belgian Blue or the Piedmontese allele from the sire at each position of the genomic region under study was also incorporated as a covariate. The interaction between chromosomal positions and the myostatin gene was estimated using SAS (SAS Inst. Inc., Cary, NC) and was reported when significant.

The experimentwise threshold value was calculated according to Lander and Kruglyak (1995). An *F*-statistic was considered suggestive of linkage if it exceeded a value of $F = 11.7$ (1 expected false-positive per genomic scan; expected number of false-positives [**ENFP**] = 0.5) and significant if it exceeded a threshold value of $F = 18.7$ (1 expected false-positive in 20 genomic scans; ENFP = 0.025). A Bonferroni adjustment was applied to the thresholds to account for testing of main effects and interactions.

Results

Regions identified in the family with Belgian Blue inheritance at least at the suggestive level are summarized in Table 1. Regions on chromosomes 3, 4, 8, 9, and 10 may contain loci associated with growth, carcass composition, and meat quality traits.

A chromosomal region with effects on marbling score (ENFP < 0.025) and retail product yield (ENFP < 0.5) were identified on chromosome 3 (Figure 1). Individuals inheriting the Belgian Blue allele had more marbling and less retail product yield than those inheriting the MARC III allele (differences between alleles of 29.2 and –1.28%, respectively).

In the same family, a QTL was identified for postweaning average daily gain and hot carcass weight on chromosome 4 (Figure 2). Individuals inheriting the Belgian Blue allele gained weight faster and were heavier than those inheriting the MARC III allele (80 g/d and 15.3 kg, respectively). This region of chromosome 4 interacted with the myostatin gene ($P < 0.001$) for

Table 1. Allelic effects of putative QTL detected with at least suggestive level on the family from the Belgian Blue × MARC III sire

Chromosome	Trait[ab]	Effect (BB – MIII)[c]	*F*	*P*[d]	Genome[e]
3	MARBLE	29.2	19.0	0.00002	0.02
	RPYD	–1.28%	12.8	0.0004	0.33
4	HCW	15.3 kg	17.6	0.00004	0.04
	ADG	0.08 kg/d	17.1	0.00005	0.05
	(WBS3)	—	12.2	0.0006	0.4
8	FAT	0.16 cm	13.1	0.0003	0.29
	MARBLE	29.9	13.4	0.0003	0.26
9	WBS14	–0.4 kg	12.25	0.0005	0.41
10	MARBLE	–32.1	11.9	0.0007	0.49

[a]MARBLE = marbling score, RPYD = retail product yield (%), HCW = hot carcass weight (kg), ADG = postweaning average daily gain (kg/d), WBS3 = meat tenderness measured as Warner-Bratzler shear force at 3 d postmortem, FAT = fat depth (cm), WBS14 = meat tenderness measured as Warner-Bratzler shear force at 14 d postmortem.

[b]Quantitative trait loci detected at least at the suggestive level, according to Lander and Kruglyak (1995). Trait within parenthesis was suggestive (expected number of false-positives ≤ 1) for the interaction between the chromosome and the myostatin gene on chromosome 2. Underscored traits were significant (expected number of false-positives ≤ 0.05); all others were suggestive (expected number of false-positives ≤ 1).

[c]BB = Belgian Blue, MIII = MARC III.

[d]Probability of false-positive for a single test.

[e]Expected number of false-positives per genomewide scan (Lander and Kruglyak, 1995).

Warner-Bratzler shear force at 3 d postmortem (Figure 3). However, no effect was observed for Warner-Bratzler shear force at 14 d postmortem in this chromosomal region. Shown in Figure 4 are the differences in performance of the four genotypic groups for Warner-Bratzler shear force at 3 d postmortem. Among animals with the active myostatin gene (+/+), those that inherited the MARC III allele in this region of chromosome 4 had a greater 3-d Warner-Bratzler shear force than those inheriting the Belgian Blue allele (5.01 vs 4.29 kg, respectively). In contrast, for animals inheriting one inactive myostatin allele (*mh*/+), animals inheriting the Belgian Blue allele were tougher than those inheriting the MARC III allele (4.96 vs 4.54 kg, respectively).

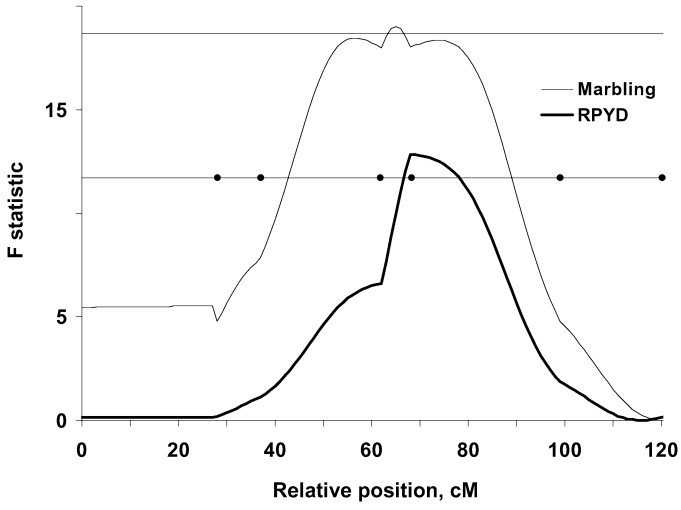

Figure 1. *F*-Statistic profile for bovine chromosome 3. Profile for marbling score (MARBLE), and retail product yield (RPYD) for the family from the Belgian Blue × MARC III sire. The upper horizontal line represents the significant threshold (*F* = 18.7), and the lower horizontal line represents the suggestive threshold (*F* = 11.7). Dots on the lower horizontal line indicate the relative position of markers BM2904, BMS819, BMS2790, BMS937, BMS835, and BMS2712.

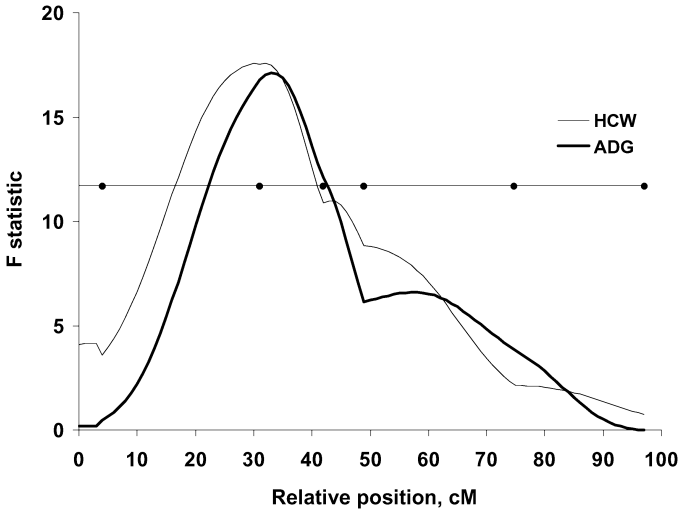

Figure 2. *F*-Statistic profile for bovine chromosome 4. Profile for hot carcass weight (HCW) and postweaning average daily gain (ADG) for the family from the Belgian Blue × MARC III sire. The horizontal line represents the suggestive threshold (*F* = 11.7). Dots on the lower horizontal line indicate the relative position of markers BL1024, BMS1237, MAF70, TGLA116, BMS1074, and BL1121.

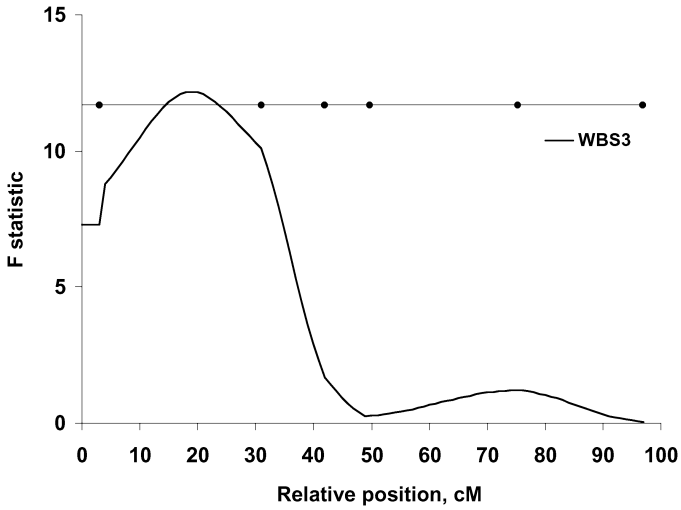

Figure 3. *F*-Statistic profile for bovine chromosome 4. Profile for meat tenderness measured as 3-d Warner-Bratzler shear force for the family from the Belgian Blue × MARC III sire. The horizontal line represents the suggestive threshold ($F = 11.7$). Dots on the horizontal line indicate the relative position of markers BL1024, BMS1237, MAF70, TGLA116, BMS1074, and BL1121.

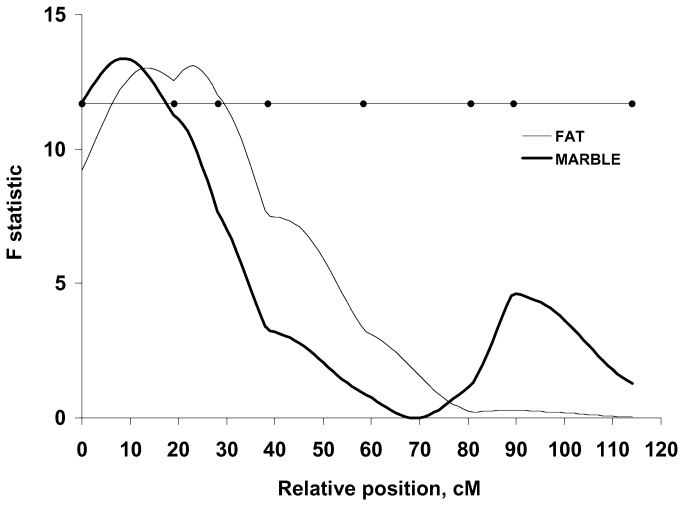

Figure 5. *F*-Statistic profile for bovine chromosome 8. Profile for fat depth (FAT) and marbling score (MARBLE) for the family from the Belgian Blue × MARC III sire. The horizontal line represents the suggestive threshold ($F = 11.7$). Dots on the lower horizontal line indicate the relative position of markers BMS1864, RM372, BM310, BMS678, BMS2072, BMS2196, SRC259, and BMS836.

In the family of Belgian Blue inheritance, evidence suggesting the presence of a QTL that affects fat depth (ENFP = 0.29) and marbling score (ENFP = 0.26) was identified on chromosome 8 (Figure 5). Individuals inheriting the Belgian Blue allele had a higher fat depth and marbling score than those inheriting the MARC III allele (the effects were 0.16 cm and 29.9, respectively).

Evidence suggesting the presence of a QTL for Warner-Bratzler shear force at 14 d postmortem and marbling score were identified on chromosomes 9 (ENFP = 0.41) and 10 (ENFP = 0.49), respectively, in the family with Belgian Blue inheritance (Table 1). Animals inheriting the MARC III allele were 0.4 kg tougher for Warner-Bratzler shear force at 14 d postmortem on chromosome 9 and had a marbling score increased by 32.1 for chromosome 10 than those inheriting the Belgian Blue allele.

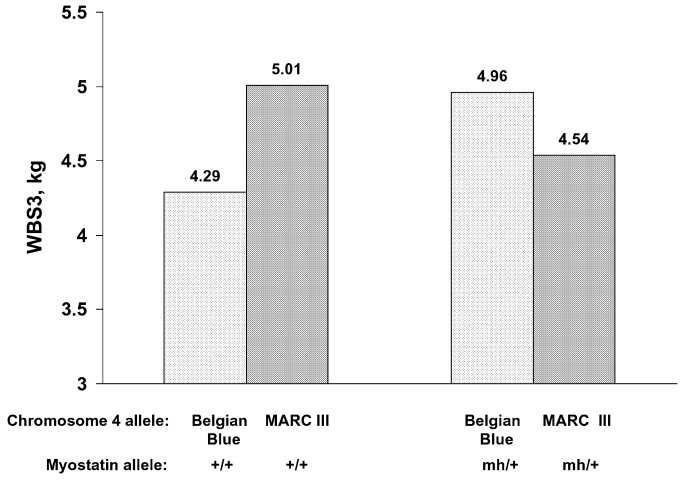

Figure 4. Interaction for meat tenderness measured as 14-d Warner-Bratzler shear force (kg), between the myostatin gene (+/+ or *mh*/+) and chromosome 4 (Belgian Blue or MARC III) for the family from the Belgian Blue × MARC III sire.

Chromosomal regions with at least suggestive support for the Piedmontese and Angus family are summarized in Table 2. A region on chromosome 8 was identified to contain evidence supporting the presence of loci associated with meat quality traits.

A centromeric region on chromosome 8 showed evidence supporting (ENFP = 0.03) the presence of a QTL for fat depth, which interacted with the myostatin gene ($P < 0.001$) on chromosome 2 (Figure 6). Figure 7 presents the performances of all four genotypic groups at the maximum of the *F*-statistic profile. Within progeny inheriting only active myostatin alleles, those that inherited the Piedmontese allele on chromosome 8 were leaner than those inheriting the Angus allele (0.7 vs 0.87 cm, respectively). Conversely, for animals inheriting the inactive myostatin allele, those inheriting the Angus allele were leaner than those inheriting the Piedmontese allele (0.46 vs 0.73 cm, respectively).

Discussion

Epistatic interactions between loci have been postulated to exist for quantitative trait loci (Falconer, 1989), and current technology allows their detection. Microsatellite markers have been successfully used to identify a region on chromosome 8 with an epistatic interaction

Table 2. Allelic effects of putative QTL detected with at least suggestive level on the family from the Piedmontese × Angus sire

Chromosome	Trait[ab]	Effect (P – A)[c]	*F*	*P*[d]	Genome[e]
8	(FAT)	—	18.4	0.00002	0.03

[a]FAT = fat depth (cm).
[b]Quantitative trait loci detected at least at the suggestive level, according to Lander and Kruglyak (1995). Trait within parenthesis was suggestive (expected number of false-positives ≤ 1) for the interaction between the chromosome and the myostatin gene on chromosome 2.
[c]P = Piedmontese, A = Angus.
[d]Probability of false-positive for a single test.
[e]Expected number of false-positives per genomewide scan (Lander and Kruglyak, 1995).

with the myostatin gene that affects fat depth. Evidence suggests that in one family there is a direct effect of the QTL on fat depth, whereas in the other family there is evidence of an interaction of the same chromosomal region with the myostatin gene on chromosome 2. In both families, those individuals inheriting the allele from the double-muscled grandsire deposited greater amounts of fat than those individuals inheriting the active myostatin allele from the granddam. This region of the genome harbors a gene that has an opposite effect on fat deposition compared with the effect of the myostatin gene. Different alleles on the chromosome 8 locus could be involved, given that one family interacted with the myostatin gene and not in the other. Epistatic interactions have been identified in other species (Li et al., 1997; Gurganus et al., 1999); however, this is the first report of such epistatic interactions in livestock. It is likely that as the ability to genotype larger populations increases, multiple interactions will be detected.

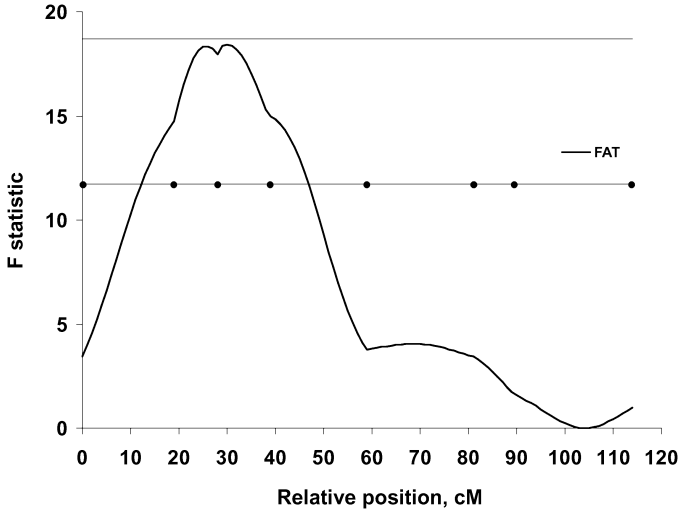

Figure 6. *F*-Statistic profile for bovine chromosome 8. Profile for fat depth for the family from the Piedmontese × Angus sire. The upper horizontal line represents the significant threshold ($F = 18.7$) and the lower horizontal line represents the suggestive threshold ($F = 11.7$). Dots on the horizontal line indicate the relative position of markers BMS1864, RM372, BM310, BMS678, BMS2072, BMS2196, SRC259, and BMS836.

A QTL for marbling score was identified on chromosome 3 from the Belgian Blue × MARC III sire. The genomic region where the locus resides has the effect of increasing marbling and lowering retail product yield in animals inheriting the Belgian Blue allele from the grandsire. A similar effect was observed for a locus residing on chromosome 27 for marbling score (Casas et al., 2000). Animals with one copy of the inactive myostatin gene tend to deposit less intramuscular fat and increase retail product yield (Casas et al., 1998). This provides an additional example that a population or breed with rather extreme phenotype (i.e., less marbling) has segregating QTL alleles with the opposite effect.

Evidence for the existence of a quantitative locus associated with hot carcass weight and postweaning average daily gain was identified near the centromeric region of chromosome 4 on the family from the Belgian Blue × MARC III sire. Individuals inheriting the allele from the Belgian Blue grandsire tend to gain weight faster and have a greater carcass weight than individuals inheriting the MARC III allele from the granddam. Alleles inherited from MARC III animals can be from any of the four breeds involved in the composite breed (Hereford, Angus, Red Poll, or Pinzgauer), so these re-

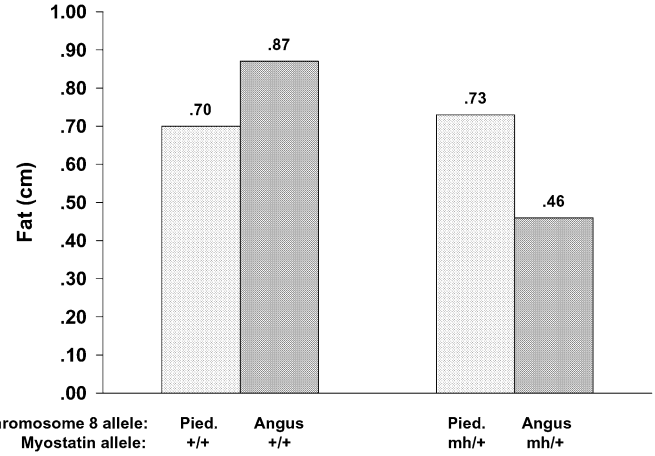

Figure 7. Interaction for fat depth (cm), between the myostatin gene (+/+ or *mh*/+) and chromosome 8 (Piedmontese or Angus) for the family from the Piedmontese × Angus sire.

sults highlight the need to characterize allelic variation of quantitative trait loci in several breeds and breed crosses to enable effective selection based on marker information.

The region on chromosome 4 where this QTL for hot carcass weight and postweaning average daily gain is located excludes the region where the leptin and insulin-like growth factor binding protein-3 (**IGFBP-3**) genes reside. Hence, genes other than leptin and IGFBP-3 are probably responsible for this effect. Houseknecht et al. (1998), in a review of the biology of leptin, indicated that improvement of carcass composition is an important goal in livestock production. The increased leptin production derived from the *Ob* gene has been associated with fat deposition in swine, but limited information is available in cattle.

Evidence of a quantitative trait loci for meat tenderness was found on chromosomes 4 and 9 in the family from the Belgian Blue × MARC III sire, and the locus on chromosome 4 interacted with the myostatin gene for meat tenderness. In a previous analysis, putative quantitative trait loci for meat tenderness were identified in the family from the Piedmontese × Angus sire on chromosomes 5 and 29 (Casas et al., 2000). Also, in animals with *Bos indicus* × *Bos taurus* inheritance, a significant QTL has been identified on chromosome 15 (Keele et al., 1999). These results suggest that different genomic regions are involved in the expression of quantitative traits, depending on the genetic background. Alternatively, it may simply be that the QTL are not segregating the relevant alleles in the families under study. To date, five different genomic regions on chromosomes 4, 5, 9, 15, and 29 have been associated with the expression of meat tenderness in cattle.

Retail product yield is an estimate of the muscle mass produced by the animal and is considered an important carcass composition trait. Evidence of a QTL affecting this trait was detected on chromosome 3 in the family from the Belgian Blue × MARC III sire. Casas et al. (2000) identified a region of chromosome 5 that contains a QTL for retail product yield in the family from the Piedmontese × Angus sire. Stone et al. (1999), using a family from a Brahman × Hereford sire, detected QTL for this trait on chromosomes 2, 13, 18, and 26. Genetic background also influences the detection of QTL for retail product yield. Four putative QTL were identified using a family from a *Bos taurus* × *Bos indicus* sire, whereas only two were detected in families from *Bos taurus* crossbred sires. Already identified regions need to be characterized in outbred populations to assess their usefulness in selection schemes.

A QTL for fat depth was detected on chromosome 8. In a previous analysis, putative QTL for fat were identified in the family from the Piedmontese × Angus sire on chromosomes 5 and 14 (Casas et al., 2000). Also, in a family from *Bos taurus* × *Bos indicus* sire, a QTL for fat thickness was detected on chromosome 2 (Stone et al., 1999). This locus on chromosome 2 is unrelated to the myostatin gene because they are more than 60 cM apart. Four different genomic regions have been associated with the expression of fat thickness in beef cattle.

Marbling score is an important trait in meat quality. Six regions on different chromosomes have been identified as harboring QTL for this trait. Three QTL were identified on chromosomes 3, 8, and 10 in the present study in the family from the Belgian Blue × MARC III sire. Two QTL were previously detected in this family on chromosomes 17 and 27 (Casas et al., 2000) and Stone et al. (1999) detected one QTL on chromosome 2. Diverse genetic background influences the expression of fat deposition traits. This underscores the need to characterize the variation of these genomic regions in other breeds and populations.

Effects of QTL expressed as residual SD units were moderate and within the expected magnitude. The effect for the QTL identified in the present scan ranged from 0.47 to 0.63 SD. Casas et al. (2000) indicated that selective genotyping, followed by the inclusion of information from the entire family, is a highly efficient procedure for identifying QTL with effects > 0.7 SD. This procedure was pursued by Casas et al. (2000) and it was expected that if other QTL were to be identified, they would have an effect of < 0.6 SD. The results from the present study are in agreement with the observation from the initial study.

The power to detect QTL of the magnitude identified in the present study is moderate and was previously determined (Casas et al., 2000). For significant QTL with an effect of 0.6 SD, the power of detection is 0.71. This was the case for marbling score on chromosome 3. The power to identify suggestive QTL with effects of 0.6 SD was 0.22. This is the case for hot carcass weight and postweaning average daily gain on chromosome 4, for meat tenderness measured as Warner-Bratzler shear force at 14 d postmortem on chromosome 9, and for marbling score on chromosomes 8 and 10. For suggestive QTL with an effect of approximately 0.5 SD (for retail product yield on chromosome 3 and for fat depth on chromosome 8), the power to identify them ranged between 0.34 and 0.35. For further analysis of these QTL, population sizes should be increased to assess their effect and magnitude.

The myostatin gene is considered a major gene because of its extreme effect on growth and carcass traits (Arthur, 1995; Casas et al., 1999). Although it is a gene with a considerable effect, other loci with more subtle effects are involved in the expression of quantitative traits. These loci were identified. The magnitude of these QTL were mostly suggestive, although a QTL was significant. New research aimed at quantifying variation at these QTL in different populations will provide a strong base from which to launch marker-assisted selection.

Implications

Quantitative trait loci for growth and carcass traits have been detected. In families with allelic segregation

of the myostatin gene in cattle, other loci also influence quantitative traits. Epistatic interactions for fat depth and meat tenderness between the myostatin gene and other regions of the genome were detected, implying that the myostatin allele may interact with a multitude of loci that influence meat quality. Regions reported here to contain quantitative traits need to be assessed in other populations to determine the extent of their usefulness in selection schemes aided by marker information.

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