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PRODUCTION AND MANAGEMENT: *Original Research*

Effects of the F94L Limousin associated myostatin gene marker on metabolic index in growing beef heifers*

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ABSTRACT

Objective: Our objective was to evaluate fasting heat production in cattle with and without the *GDF8* mutation.

Materials and Methods: The heifers used in this study were genotyped for the myostatin (*MSTN*) gene mutation to determine their *MSTN* genotype as either homozygous normal for phenylalanine at amino acid position 94 of *MSTN* (0 copy; n = 5) or homozygous for F94L variant in *MSTN* (2 copy; n = 6). Oxygen consumption was measured using portable headbox respiration calorimeters, and heat production was calculated.

Results and Discussion: Body weight was not different between treatments ($P = 0.33$), but it did differ across days ($P < 0.01$), increasing as heifer age increased. Oxygen consumed in liters per kilogram of metabolic BW was greater for 0 copy heifers than the heifers with 2 copies of the F94L *MSTN* variant ($P = 0.03$), on all days measured. Oxygen consumed and heat production decreased as heifer age increased in all heifers irrespective of genotype ($P \leq 0.03$). Respiratory quotient had a tendency to be greater for heifers with 2 copies than for heifers with no copy ($P = 0.07$). Average daily gain measured across the whole study (121 d) was greater for heifers with 2 copies of the F94L *MSTN* variant.

Implications and Applications: Therefore, it is likely that cattle with 2 copies of the F94L *MSTN* substitution have lower maintenance energy requirements than cattle without the *MSTN* gene. Thus, genotype, if known, should be considered when assessing energy requirements of beef cattle.

Key words: cattle, heat production, myostatin genotype

INTRODUCTION

In the beef industry, it would be beneficial to determine the effects of single nucleotide polymorphism associations and to determine whether associations with different single nucleotide polymorphisms interact to cause important genotypic or phenotypic changes. At the US Meat Animal Research Center, we have a unique population of cattle (MARC I) that is a composite breed of 1/4 Limousin, 1/4 Braunvieh, 1/4 Charolais, and 1/4 Angus-Hereford. Within this population, an allele for the myostatin gene (GDF8), which influences protein accretion, was selected. Double muscling in cattle is the result of an inactivating mutation in the GDF8 myostatin (*MSTN*) gene (Casas et al., 2000). Double-muscled animals have leaner carcasses with greater muscle mass and less fat than animals without the mutated *MSTN* gene (Casas et al., 2000) and have a greater capacity to synthesize muscle protein (Koohmaraie et al., 2002). A GDF8 mutation (leucine substitution at the F94 position; BTA2; rs110065568) prevalent in Limousin (Grobet et al., 1998) also increases muscling and reduces fat but is less extreme than double-muscling mutations found in Belgian Blue or Piedmontese breeds (Bennett et al., 2010). This *MSTN* variant is important to study because of its extreme effect on growth and carcass traits (Casas et al., 2000). In finishing cattle, the *MSTN* variant has been reported to reduce fat thickness, produce a larger ribeye area, and have a better YG (Bennett et al., 2019).

The heifers used in this study were genotyped for the *MSTN* gene mutation to determine their *MSTN* genotype

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The authors declare no conflicts of interest.

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as either homozygous normal (*CC*) for phenylalanine at amino acid position 94 of *MSTN* (0 copy; n = 5) or homozygous (*AA*) for F94L variant in *MSTN* (2 copy; n = 6).

Our objective was to evaluate fasting heat production in heifers with and without the GDF8 mutation.

MATERIALS AND METHODS

All animal use protocols were approved by the US Meat Animal Research Center Animal Care and Use Committee (Approval # 3040-3100-092).

The frequency of the leucine allele (L) of the *MSTN* F94L single nucleotide polymorphism previously reported by Grobet et al. (1998) and Cushman et al. (2015) was increased to intermediate levels by selection resulting in similar numbers of each homozygote available for study. Briefly, the L allele substitutes for phenylalanine at the 94th amino acid of *MSTN* (BTA2; rs110065568). Eleven heifers (264 ± 10.3 kg of initial BW) born between March 31 and May 26, 2012, were used during the study based on their genotypes. After weaning on September 24, 2012, the heifers were treated for any health issues and placed on a forage-based diet. The heifers were genotyped for the *MSTN* gene mutation to determine which were their *MSTN* genotype as either homozygous normal (*CC*) for phenylalanine at amino acid position 94 of *MSTN* (0 copy; n = 5) or homozygous (*AA*) for F94L variant in *MSTN* (2 copy; n = 6). Genotyping was performed using a primer extension method with mass spectrometry–based analysis of the extension products on a MassArray system as suggested by the manufacturer (Sequenom, Inc., San Diego, CA) and described previously (Stone et al., 2002). Genotype quality control was performed using pedigree and genotype information analyzed through GenoProb (Thallman, 2002) and conducting amplicon-based next generation sequencing in the region of interest.

The composites cattle population used in the current experiment was formed starting in 1978. From 1992 to 1999 the composite breed was split into 2 lines: a calving ease selection line and a control line (Bennett et al., 2010). After the completion of the selection experiment, cows from both genetic lines were bred to the same bulls and their progeny treated as a single population. During this period from 2000 to 2006, the MARC 1 population produced approximately 250 calves from 18 sires each year. Approximately one-half of the sires were replaced each year, resulting in the use of 68 bulls selected from within the herd. Thus, there have been several generations since forming the composite MARC 1 breed, and multiple sires were used in the formation and propagation of the composites. Because of the number of generations and sires between the formation of the composite and this experiment, there was ample opportunity for most of the linked Limousin background to disassociate from the mutation, except for very closely linked genomic variants. It is possible that this mutation is not causal and there is another causal mutation of Limousin origin in nearby linkage disequilibrium with the *MSTN* gene variant. However, it is highly unlikely for an association of this mutation with the broader Limousin genome.

Heifers were fed daily at 0800 h throughout the experiment and had ad libitum access to fresh water at all times, which included the fast and while gas exchange was being collected in the head box. The diet consisted of (all on a DM basis) 67.3% corn silage, 27.0% alfalfa hay, 5.5% dry-rolled corn, and 0.2% salt. A high-forage diet was used during the experiment to grow the heifers slowly and simulate a replacement heifer growth curve. The heifers were fed slightly above a maintenance level of intake to allow for growth (approximately 1.5 times maintenance).

In November of 2012, the heifers were moved to partially covered concrete pens (3.7 m × 24.7 m; 4 heifers per pen) open to the south. They were acclimated to close human contact for a period of 4 wk. After the acclimation to close human contact, the heifers were moved into individual metabolism stanchions (87 cm × 214 cm) in an enclosed barn and adapted to the metabolism facility and the head boxes. The metabolism facility and head box adaptation occurred over a period of 6 wk, gradually increasing the amount of time the heifers spent within the metabolism stanchions and head boxes. The heifers were adapted to the facility and head boxes before the first measurement of fasting heat production.

Before the gas collections, ethyl alcohol recoveries were determined by burning 100% ethyl alcohol in the sealed head box and assessing the total gas concentration collected during this time. The alcohol recoveries ranged between 98 and 102% in all head boxes. Temperature and dew point inside the head box were recorded every minute using a temperature probe and relative humidity probe (Model TRH-100, Pace Scientific Inc., Moorseville, NC) connected to a data logger (Model XR440, Pace Scientific Inc.). Line pressure was measured from a manometer (Item #1221-8, United Instruments, Westbury, NY), and barometric pressure of the room was recorded using a barometer (Chaney Instruments Co., Lake Geneva, WI). Total volume of gas was measured using a gas meter (Model AL425, American Meter, Horsham, PA), and continuous proportional samples of outgoing and incoming air were diverted to polyethylene-aluminum-Mylar laminate collection bags (61 × 61 cm, 44 L; PMC, Oak Park, IL) by a glass tube rotameter (Model 1350E Sho-Rate "50," Brooks Instruments, Hatfield, PA). Then, the collected gas samples were analyzed to determine their composition according to Nienaber and Maddy (1985) and corrected for pressure and temperature within the box. Heat production was calculated according to Kleiber (1975) from liters of O_2 consumed and the respiratory quotient (**RQ**).

For the collection of fasting heat production, heifers were fasted for 56 h but had ad libitum access to fresh water during the fast. The heifers were then placed in the head boxes, the doors were closed, and at least 3 air turnovers were allowed inside the head box before the gas was collected. Based on methane production (less than

Table 1. Influence of the F94L myostatin variant on BW, oxygen consumption, and respiratory quotient in fasted MARC I heifers[1]

	Heifer age, d				*P*-value[4]	
Item[2]	205	261	326	SEM[3]	Treatment	Day
BW, kg						
0 Copy	210	275	315	14.9	0.33	<0.01
2 Copy	216	299	345	16.3		
O_2, L/kg of metabolic BW						
0 Copy	21.3	18.8	15.0	1.11	0.03	<0.01
2 Copy	17.3	15.3	11.7	1.01		
CH_4, L/d						
0 Copy	2.49	2.96	2.13	0.408	0.89	0.88
2 Copy	2.50	2.29	2.68			
RQ[5]						
0 Copy	0.76	0.82	0.86	0.016	0.07	<0.01
2 Copy	0.84	0.86	0.83	0.015		
HP,[6] kcal/d						
0 Copy	5,499	6,077	5,364	183.2	<0.01	<0.01
2 Copy	4,742	5,353	4,520	167.2		
HP,[6] Mcal/kg of metabolic BW						
0 Copy	101.5	91.2	73.5	5.39	0.03	<0.01
2 Copy	84.4	74.8	59.2	4.93		

[1]Heifers were fasted for 56 h before being placed in the head box calorimeters.

[2]The 0 copy is homozygous *CC* at position *GDF8*c.433 (NM_001001525), which results in the wild type phenylalanine (F) at position 94 of the myostatin protein. The 2 copy is homozygous *AA* at position *GDF8*c.433, which results in a leucine (L) at position 94 (F94L) of the myostatin (MSTN) protein (Esmailizadeh et al., 2008).

[3]Largest SE of the LSM.

[4]Observed significance levels for genotype comparisons.

[5]RQ = respiratory quotient, genotype × day interaction tendency present ($P = 0.06$).

[6]HP = heat production, calculated according to Kleiber (1975), where HP = [(RQ × 27 + 87)/22.4] × O_2 consumption in liters per day.

3 L/d), the length of fast was considered to be sufficient to allow the heifers to be in a postabsorptive state. Fasting heat production was measured 3 times throughout the experiment at 205, 261, and 326 average days of age for the heifers. Heat production was calculated from RQ and liters of oxygen consumption according to Kleiber (1975).

After measurement of fasting heat production, the heifers were moved back to their pens and fed ad libitum bromegrass hay for 24 h, after which they were offered the previously mentioned diet that was split fed 4 times per day for 7 d to prevent acidosis.

All data were analyzed using the PROC MIXED procedure in SAS 9.3 (SAS Institute Inc., Cary, NC). Model fixed effects included allele, day, and allele × day interaction. Heifer was included as a random effect. Day was a repeated term with heifer as the subject. Means were calculated using the LSMEANS option, and the pdiff function was used to separate genotype means. Effects were considered significant at a *P*-value of ≤ 0.05, with tendencies declared at *P*-values between 0.05 and 0.10.

RESULTS AND DISCUSSION

Body weight (Table 1) was not different between treatments ($P = 0.33$), but it did differ across days ($P < 0.01$), increasing as heifer age increased. The increase in BW was expected because the heifers were not mature at the time of the study, and slight growth and BW gain were expected as they were fed near 1.5-times maintenance.

Oxygen consumed in liters per kilogram of metabolic BW (**MBW**) was greater for 0 copy heifers than the heifers with 2 copies of the F94L *MSTN* variant ($P = 0.03$), on all days measured. The reduced oxygen consumption on a MBW basis is plausible because cattle with the *MSTN* variant typically have a reduction in internal organ size (Kambadur et al., 1997). If the liver accounts for 50% of the oxygen consumed by the digestive tract (Huntington and Reynolds, 1987), it is reasonable that we detected a difference in total body oxygen consumption, because heifers with 2 copies may have had a smaller liver. Oxygen consumption by the gastrointestinal tract varies among

cattle type and stage of production and is typically increased by level of energy consumption. It is interesting that the fasting heifers in the current experiment had such large differences in oxygen consumption because fasting reduces gastrointestinal-tract oxygen consumption by approximately 30% (Huntington and Reynolds, 1987), and these heifers had been fasting for 56 h when placed in the headbox calorimeters.

Research using *MSTN* knockout mice has shown a decrease in mitochondrial content and changes in mitochondrial respiratory function (Ploquin et al., 2012). The capacity for oxidative metabolism is also dependent on mitochondrial content and can also be decreased (Ploquin et al., 2012). Thus, if mitochondrial respiration is decreased without *MSTN*, in the present experiment decreases in oxygen consumption in the 2 copy heifers could be a result of lesser mitochondrial content and lesser mitochondrial respiration (although not directly measured).

Perhaps the reduction in total body oxygen consumption is also related to respiration ability. It has been noted that double-muscled cattle are early maturing, as evidenced from bone weights (Shahin and Berg, 1985). Cattle with double-muscling phenotypes typically have more muscle mass in the proximal parts of the limbs relative to the fibrous muscle more distal on the limbs (Shahin and Berg, 1985). Thus, they have heavier rib bones due to muscle hypertrophy, and double-muscled cattle have been reported to have a reduction in muscles associated with respiration (Shahin and Berg, 1985), realizing that respiration is both exhaled volume and respiration rate. Therefore, our data coincide with those of Shahin and Berg (1985), where cattle with 2 copies of the F94L *MSTN* variant also had decreased respiration ability as evidenced with their decrease in oxygen consumption; however, respiration rate was not measured.

Additionally, oxygen consumed (L/kg of MBW) and heat production (Mcal and Mcal/kg of MBW) decreased as heifer age increased in all heifers irrespective of genotype ($P \leq 0.03$). This was expected as metabolic rate typically decreases as cattle age and growth rate slows. Lambs on a high and low level of feed intake (at the same dietary ME concentration) had decreased heat production as they aged (Freetly et al., 2002). Likewise, heifers on a high and low level of feed intake also exhibited decreased heat production as they aged (Freetly et al., 2003). Furthermore, Freetly et al. (2002) reported that the amount of heat produced per unit of MBW is influenced by age, genetic background, and previous plane of nutrition. Heat production is generally used as an index of energy required for maintenance (Blaxter, 1962). Many previous studies reported that metabolic rate was greater in younger animals than in mature animals (Blaxter, 1962; Freetly et al., 2002; Freetly et al., 2003), and Brody (1945) noted that the proportion of liver and intestine weight to total BW decreases with increased BW in maturing animals. The difference in heat production observed between heifers with 0 and 2 copies of the F94L *MSTN* substitution are likely a function of the difference in mature weight and rate of attainment of maturity. The heifers with 2 copies of the F94L *MSTN* gene variant may approach maturity more rapidly than heifers with 0 copy of the *MSTN* gene. Myostatin interferes with protein synthesis and protein degradation in myofibers (Trendelenburg et al., 2009). The decreased heat production observed in the heifers with 2 copies of the F94L *MSTN* gene variation could suggest that protein turnover is altered, potentially where protein degradation is decreased. No change in protein synthesis, with a corresponding decrease in protein degradation, would decrease heat production, as was noted in heifers with 2 copies of the F94L *MSTN* gene variant in the present experiment.

Methane production did not differ across genotype ($P = 0.89$) or day ($P = 0.88$). Methane production can be used as an index of ruminal fermentation, because methane production is decreased to negligible values during fasting (Blaxter, 1962). These low levels are indicative of a postabsorptive state, and by the third and fourth day of fasting in cattle, methane production is typically less than 2 L in 24 h (Blaxter, 1962). Methane production measured in the present study averaged 2.5 L over the 24-h measurement period across all treatments and days. Therefore, our heifers did reach a postabsorptive state.

Respiratory quotient had a tendency to be greater for heifers with 2 copies than for heifers with no copy ($P = 0.07$). An RQ of 0.7 typically indicates a fasting animal (Brody, 1945). It is unknown why the heifers with 2 copies of the *MSTN* variant tended to have a greater RQ than heifers with 0 copies, but this does not support the idea that cattle with the *MSTN* gene have decreased respiratory ability. The average RQ for the 0 copy versus 2 copy heifers was 0.81 and 0.84, respectively. There is likely no real biological difference in these RQ.

Table 2. Average daily gain over the 121-d study for MARC I heifers[1]

Item	ADG, kg	SEM[2]	*P*-value
0 Copy	0.86	0.076	0.10
2 Copy	1.06	0.084	

[1]Heifers were weighed after the 56-h fast and after being in the head box calorimeter for 24 h; an average of the 2 weights was used to compute ADG. The 0 copy is homozygous *CC* at position *GDF8*c.433 (NM_001001525), which results in the wild type phenylalanine (F) at position 94 of the myostatin protein. The 2 copy is homozygous *AA* at position *GDF8*c.433, which results in a leucine (L) at position 94 (F94L) of the myostatin (MSTN) protein (Esmailizadeh et al., 2008).

[2]Largest SE of the LSM.

Average daily gain (Table 2) measured across the whole study (121 d) was greater for heifers with 2 copies of the F94L *MSTN* variant. Interestingly, with decreased O_2 consumption and decreased heat production combined with increased ADG, it is likely that these heifers had decreased maintenance energy requirements. It is also likely that the maintenance energy requirements decreased with age, irrespective of genotype treatment. This concept is generally accepted (NASEM, 1996). In cattle, Blaxter and Wainman (1966) reported that age influenced maintenance energy requirements less than BW. Conversely, Vermorel et al. (1980) noted that maintenance requirements changed little between 1 and 8 mo of age. Carstens et al. (1989) reported a 6% decrease in fasting HP and an 8% decrease in metabolizable energy required for maintenance between 9 and 20 mo of age.

Cattle with greater mature size typically have greater ADG (Tatum et al., 1986), which was noted in the present experiment for heifers with 2 copies of the *MSTN* gene variant. Together, the greater ADG and decreased O_2 consumption and heat production could indicate that heifers with 2 copies of the F94L *MSTN* variant did approach maturity more rapidly than heifers without the 0 copies of the gene variant.

APPLICATIONS

Oxygen consumption and heat production were less for heifers with 2 copies of the F94L *MSTN* variant, whereas the respiratory quotient tended to be greater. Therefore, it is likely that cattle with 2 copies of the F94L *MSTN* substitution have lower maintenance energy requirements than cattle without the *MSTN* gene. Thus, genotype, if known, should be considered when assessing energy requirements of beef cattle.

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