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The relationship between the myostatin gene and calving ease in beef cattle: a review of published research literature

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Abstract

Double muscling is a hereditary genetic syndrome affecting cattle, and is most notably characterised by the extreme hypertrophy of muscles, occurring in most breeds of cattle. While the double-muscled phenotype has the benefit of increased yield over the hook with a larger percentage of higher priced cuts, it is also associated with reproductive issues. The relationship between double muscling and calving ease has been well documented, with a general consensus that the homozygous affected - genotype - with two mutated myostatin alleles - is unfavourable for calving ease and birth weight compared to heterozygous and normal contemporaries. Calving difficulty in double muscled cattle is related to a morphological imbalance between the dam and calf at time of birth, where the calf width and weight is increased in homozygous affected calves, or a decrease in the pelvic area of the dam, or both depending on the mating. Carriers of the double-muscling gene are not significantly different for calving ease compared to normal cattle, but performed significantly better for post-birth production traits. For commercial beef production these findings indicate the usefulness of genomic testing for the identification of individuals with double-muscling alleles, allowing mating schemes to be built to maximise production of heterozygous animals to benefit from improved yield and avoid reproductive disadvantage.

Introduction

Double muscling (DM), or muscular hypertrophy, is a syndrome affecting cattle characterised phenotypically by hypertrophied muscles, reduction in fat and reduction of skeletal weight (Arthur, 1995). The DM phenotype involves a mutation of the myostatin gene, which results in loss of function of the negative regulator of muscle growth (Grobet et al., 1998; Kišacová et al., 2009). The myostatin gene is located on chromosome 2, and involves at least five different variations of mutation to produce the DM phenotype (Grobet et al., 1998).

While DM cattle have the benefit of increased yield over the hook, and the ability to produce a higher percentage of premium cuts (Casas et al., 1998; Fiems, 2012), the DM syndrome is also reported to be associated with various reproductive issues (Arthur et al., 1988).

The objective of this review was to examine the relationship between DM and calving ease in beef cattle, as documented in published research literature.

Identity

The double muscled allele and its normal allele have been described using many symbols in the literature (Arthur, 1995). The symbols used in this review are *dm* or *n*, where *n* represents the normal allele. Hence, the genotypes are represented as follows:

Homozygous (normal) *n* × *n*
Heterozygous (carrier) *dm* × *n*
Homozygous (DM phenotype) *dm* × *dm*

Breed

It is well documented that the breeds showing the highest occurrence of the double-muscled syndrome are Belgian Blue and Piedmontese cattle breeds (Arthur, 1995). The DM mutation has also been observed in most other cattle breeds (Arthur et al., 1988; Arthur 1995).

The DM phenotype observed can be caused by different mutations of the myostatin gene, depending on the breed. This phenomenon is called allelic heterogeneity. Grobet et al. (1998) reported on at least five different variations of DM mutation, including *nt821(del11)*, *C313Y, Q204X, F94L* and *E226X*, arising from various base deletions and substitutions. Piedmontese cattle are affected by the *C313Y* mutation (Kambadur et al., 1997), whereas the same DM phenotype in Charolais is produced by the *Q204X* mutation (Kišacová et al., 2009).

Breeds affected by the same mutation can present the DM phenotype differently, both between breeds and within breed (Ménissier, 1982; Goyache, 2002). The mutation *nt821(del11)* affects both Belgian Blue and Asturiana de los Valles (Dunner et al., 1997), but the extent to which the DM phenotype is expressed differs between the breeds with the Belgian Blue DM phenotype being the more extreme of the two breeds.

Data set size

Data set size reported in published research literature generally range between 200-400 animals (see Table 1), and seems to be limited by herd size. While the dataset size does not seem particularly large, the findings are consistent across studies, as shown in Table 1.

Traits recorded

Calving related traits have been recorded concurrently with traits such as 200 day weight, 400 day weight and various carcase traits in some studies to 'weigh up' the advantages and disadvantages of the DM phenotype in a given herd.

The DM trait has been recorded by either phenotypic appraisal, or using genotyping technology. The method of assessing *dm* allelic frequency in a test population in any given study has been more or less informed by the publication year. The reason for this is that the technology and knowledge needed to genotype large numbers of cattle was simply not available for use in the earlier studies, or it was not economically viable for an entire herd.

Publication year

As noted by Wiener et al. (2002), any results relating to DM syndrome published prior to 1990 need to be approached with caution as the detection of the *dm* × *dm* affected genotype was based upon visual appraisal of muscling score and not based on actual genotyping. Phenotypes for the DM trait are relatively continuously distributed (Grobet et al., 1998; Goyache et al., 2002) and as such there is some difficulty in classifying animals for this trait. This may have led to inaccurate estimates of allelic effects due to false negative and/or positive identification.

Casas et al. (1998) was one of the first studies where genetic markers were employed to assess allelic frequencies, with six microsatellites being used to asses carriers and non-carriers of the mutated gene. The results were consistent with previous non-genomic studies, with calving ease decreasing considerably in *dm* × *dm* calves compared to both *dm* × *n* and *n* × *n* animals.

While the ability to correctly classify 100% of DM animals and therefore allelic frequency is less important for discovering overall trends, it becomes more important in ascertaining the mode by which the DM allele is inherited (Grobet et al, 1997).

Mode of Inheritance

The mode of inheritance of DM has been hotly contested (Arthur, 1995), though this is most likely confounded with the inability to correctly classify animals from phenotypic appraisal alone. Weiner (2002) found that, in a genotyped South Devon herd, the *dm* allele had additive effects on muscling score and fat depth, but was recessive for calving difficulty.

Calving Ease

Casas et al. (1999) studied genotyped Piedmontese cross animals and reported a significant increase in assisted calvings of *dm* × *dm* calves compared to their *dm* × *n* and *n* × *n* contemporaries, with no significant difference in number of assisted calvings between *dm* × *n* and *n* × *n* calves. This suggests that two copies of the mutated myostatin gene are unfavourable for calving ease. Kišacová et al. (2009) corroborate the finding that the DM allele has no effect on calving ease in genotyped animals, though it should be noted that there were no homozygous affected *dm* × *dm* calves in the study and as such the effect of two copies of the mutated myostatin gene was not reported on.

Studies based on phenotypic classification were broadly similar in their findings to genotyped studies, as presented in Table 1.

Conformation

Calving difficulty in DM cattle is related to a morphological imbalance between the dam and calf at time of birth (Hanset and Jandrain, 1979). The imbalance occurs both in affected dams and in affected calves. Double muscled animals have a modified growth curve compared to normal cattle whereby they have a higher birth weight and lower adult weight (Ménissier, 1982).

The DM phenotype affects dam conformation, with a reduction in the size of the skeleton especially at the pelvic girdle and a more angular convergence of the iliac branches of the hip bone (Vissac et al. as cited in Arthur et al., 1988). The gradient of hypertrophy of muscles and hypotrophy of the skeleton in DM cattle is illustrated in Figure 1, indicating that the bones become smaller toward the rump/hip. The narrowing of the pelvic opening of DM dams is likely to be at least partly responsible for the notable increases in calving difficulty compared to normal cows (Arthur et al., 1988).

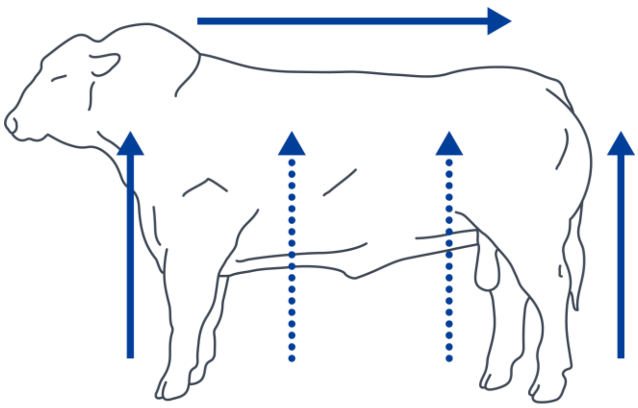

Figure 1 Gradients of muscular hypertrophy and skeletal hypotrophy in double muscled cattle (solid line represents muscular, dotted line represents skeletal)

This is further complicated as the expression of the DM gene is initiated during foetal development (Kambadur et al., 1997), increasing the width of the calf especially around the thigh and hip bone area (see Figure 1; Hanset and Jandrain, 1979; Arthur et al., 1988), and increasing the overall calf weight (Hanset and Jandrain, 1979; Cushman et al., 2015), which is not conducive to ease of calving. The larger size of the calf is problematic for normal dams, but is compounded in DM dams as they have a smaller pelvic opening, making delivery more difficult or impossible. Wiener et al. (2002) suggested that the calf’s genotype was more important in determining calving ease than that of the dam.

Table 1 Summary of research relating myostatin to calving traits

Author(s)	Year	Breed	Data Size	Traits	Country	Allele ID	Summary
Arthur, Makarechian & Price	1988	Hereford x Angus x Charolais	247 calvings	Calf birth weight Cow condition at calving Pelvic opening	USA	Phenotype	Incidence of dystocia was higher among the double-muscled than the normal cows (19% vs 6%, P<0.05). A higher incidence of dystocia was associated with phenotypically muscular calves *dm* × *dm*. Heterozygous animals did not show any increase in calving difficulty compared to normal animals. Height, width, and area of pelvic opening in DM dams were significantly smaller (P<0.05) compared to normal dams. This indicates that the higher incidence of dystocia and perinatal mortality in DM cattle can be partially attributed, to the narrow pelvic opening in DM cattle.
Arthur, Makarechian, Price & Berg	1989	Angus, Charolais, Galloway and Hereford	491 matings, 389 calvings	Calving ease Calves born & weaned Calf weight	USA	Phenotype	The DM cows had higher incidence of calving difficulty compared to normal cows.
Blasi, Lamm, Tatum & Brinks	1991	Crossbred beef dams to Piedmontese, Gelbvieh and Red Angus sires	72 female, 82 male calves	Birth weight Calving difficulty Weaning weight	USA	Phenotype	Piedmontese and Gelbvieh sired calves had a higher calving difficulty score than the Red Angus sired calves, though the difficulty scores still fell between 1 (no difficulty) and 2 (minor difficulty with some assistance). The Piedmontese sire was selected for the double muscling trait based on phenotypic appraisal. Birth weight and calving difficulty were not significantly different between Piedmontese and Gelbvieh sires calves, indicating that calves heterozygous for DM do not affect these reproductive traits significantly compared to normal calves.
Casas, et al.	1998	Belgian Blue cross and Piedmontese cross	455 (¼ BL, 209 ¼ PM)	Calving ease Birth weight Rib eye area Retail product yield Marbling Fat thickness Estimated KPH	USA	DNA	Cattle with a DM allele had increased ($P < .01$) rib eye area, retail product yield, and birth weight and decreased marbling, fat thickness, and estimated KPH, compared with those without the affected allele. There were no effects ($P > .10$) for calving ease.

Casas, Keele, Fahrenkrug, Smith, Cundiff, & Stone	1999	Piedmontese cross	301	Birth weight Weaning weight Yearling weight Assisted calving	USA	DNA	Heterozygous animals were heavier than normal animals. *dm* × *dm* calves increased 19 ± 6 % of assisted calving compared to heterozygous animals, and 21 ± 6 % compared to normal animals. The heterozygous and normal calves had a similar proportion of unassisted calving.
Wiener, Smith, Lewis, Woolliams & Williams	2002	South Devon	321 (244 females, 77 males)	200 & 400d weight Muscle score Muscle depth Fat depth Calving difficulty	UK	DNA	Two copies of the DM allele significantly increased muscle score and calving difficulty and decreased fat depth. Calving difficulty may be a function of the dam's genotype as well as that of the calf. The *dm* × *n* and *n* × *n* dam groups were very similar, supporting the view that the calf's myostatin genotype is more influential than that of its dam in determining calving difficulty.
Kišacová, Kúbek, Meluš, Čanakyová & Řehout	2009	Charolais	128 (96 Females, 32 males)	Birth Weight Calving ease	Hungary	DNA	Heterozygous calves were slightly heavier at birth, with no association with calving ease. There were no homozygous affected animals in the study due to the nature of the mating program.
Cushman et al.	2015	MARC I (Angus, Hereford, Braunvieh, Limousin, Charolais)	146 females	Calf weight	USA	DNA	Myostatin DM mutation affected birth weight in an additive fashion. Myostatin decreased the proportion of pubertal heifers at the start of the breeding season compared to normal heifers, with no effect on conception or pregnancy rates in the first breeding season.

Both issues (from dam, calf, or both) result in fetopelvic disproportion, which has been described as "foeto-maternal morphological imbalance at calving" (cited in Arthur et al., 1988).

Also associated with *dm* × *dm* calves was a higher incidence of postpartum mortality (cited in Arthur, 1995). This may be attributed to increased calving difficulty, leading to weaker calves. Other physical abnormalities reduce calf viability such as enlarged tongues of calves making sucking difficult, and rickets (cited in Arthur, 1995). Sucking difficulty can also arise from DM dams with enlarged teats and very little colostrum after calving (Arthur et al., 1988).

Production Traits

While in most breeds the disadvantage of calving difficulty has led to a heavy selection against double muscling, there can be some economic instances when selecting for one DM allele can be beneficial for yield and percentage of higher priced cuts.

Casas et al. (1998) studied genotyped beef cattle, and found that even one copy of the DM allele increased rib eye area, retail product yield, and birth weight, and decreased fat thickness and estimated KPH, compared to calves without the affected allele, with no effect for calving ease. This indicates that calves heterozygous for the double-muscle gene are superior to normal cattle in terms of productivity, and have calving ease comparable to that of calves without the allele. These findings are corroborated in the literature (Blasi et al., 1991; Casas, et al., 1998; Casas, et al., 1999; Wiener et al., 2002).

The understanding that genotyped carriers of the DM gene had a calving ease comparable to that of their normal contemporaries (i.e. no effect) is significant in that it is possible to benefit from improved production traits (e.g. yield and percentage of premium cuts) and avoid losses to reproduction in a commercial beef production scenario.

Genotyping

Single Nucleotide Polymorphism (SNP) chip genotyping of livestock has enabled parentage verification as well as identification of genes coding economically important traits that are heritable (Johnston, Tier & Graser, 2012). Genotyping using primers for mutations described by Grobet et al. (1998) can be used to identify animals that are carriers, affected or normal for the DM gene. Testing for myostatin alleles can be an effective tool for managing matings to produce heterozygous offspring.

Conclusion

Double muscling is a hereditary genetic syndrome that negatively affects calving ease in beef cattle when two copies of the mutated myostatin gene are present. Calving difficulty is related to a morphological imbalance between the dam and calf at time of birth, with increased calf weight and width, and decreased dam pelvic area. DM carriers are not significantly different to their normal contemporaries for calving ease, but perform better for post-birth production traits.

Implications

The use of genomic testing in beef production systems permits the identification of individuals with double-muscling alleles, allowing mating schemes to be built to maximise production of heterozygous animals. This marker-assisted selection approach would produce calves with higher yielding carcasses, and no effect on calving ease.

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