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Application of *Myostatin* in Sheep Breeding Programs

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Abstract: *Myostatin* or, growth and differentiation factor 8 (GDF8), has been known as the factor causing double muscling phenotype in which a series of mutations make the *myostatin* protein inactive and hence can not regulate deposition of muscle fibre. This phenotype happens at a high frequency in one breed of sheep known as the Texel. Quantitative trait loci (QTL) studies shows that a portion of the OAR2 that encompasses GDF8 has a major effect on the muscular growth in the Belgian Texel, on the muscling and fat depth in the New Zealand Texel sires, UK Texel and Charollais sheep. The functional polymorphism resides inside the GDF8 non-coding region. To date, there have been studies showing biallelic SNPs with significantly different allelic frequencies between the hyper-muscled Texel and control animals including one in the 3'UTR (g.+6223G>A) and one in 2.5 kb upstream from the GDF8 transcription start site (g.-2449G>C). The GDF8 allele of the Texel sheep is characterized by one G to A transition in the 3'UTR creating a target site for mir1 and mir206 which are highly expressed in skeletal muscle. This prevents *myostatin* gene translation and thus contributes to the Texel sheep muscular hypertrophy. Therefore, the GDF8 g.+6223A allele seems to be a causative variable of increasing muscularity in the Texel rams and could be identified as a quantitative trait nucleotide.
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1. Introduction

The first description of sheep muscular hypertrophy was introduced by Nserland (1940). This phenotype happens at a high frequency in one breed of sheep known as the Texel. Texel sheep are famous for their exceptional ability for meat production (Clop et al., 2006). Beltex and Texel sheep are both renowned for their extraordinary meatiness (Banks, 1997, Busboom et al., 1999). The Texel has become the dominant terminal-sire breed in Europe. The muscular hypertrophy phenotype (MH) shows an extraordinary muscle growth as can be shown in Figure 1.

Different authors have used different symbols to differentiate between the double muscled phenotype and the normal phenotype. These differences include double muscled or normal, DM or N, D or n, DM or dm, C or N, c or n, A or a, and mh or + (Bellinge et al., 2005).

The characterization of this phenotype includes an exaggerated overdevelopment of the muscles which is especially obvious on the hind quarters, similar to the DM condition known in the cattle (Nserland, 1940). The muscular hypertrophy phenotype in both sheep and cattle are mostly similar. The MH phenotype is characterized by muscles hypertrophy, mostly in the proximal fore- and hind quarter regions, prominent muscular protrusion with intermuscular boundaries and clearly visible grooves (Menissier, 1982, Bellinge et al., 2005). Other major characteristics, we can name thinness of the limb bones, less developed external genitalia and enlarged tongues in the newborn calves (Kieffer and Cartwright, 1980, Bellinge et al., 2005). MH animals also have less bone, less fat and more muscle with a higher proportion of _expensive_cuts of meat (Menissier, 1982, Shahin and Berg, 1985). However, there are some disadvantages of the MH phenotype in cattle including reduced fertility, low calf viability, increased stress susceptibility (Arthur et al., 1988) and dystocia (Arthur et al., 1989). Lambing difficulty (Dystocia) is a common concern amongst the sheep breeders in their consideration of the Texel (Keynes, 1994, Keynes, 1997, McMaster, 1994).

History of Texel muscular hypertrophy Sheep

The Texel has been an ideal example of the MH condition in sheep. The Texel sheep originated

from the Texel isle, the largest island of the Frisian Islands off the north coast of the Netherlands. During the mid-1800, Lincoln and Leicester long wool were crossed with the Texel breed (Mason, 1996, Onan, 2000).

Figure 1. An example of a Texel double muscle sheep.

Since 1930, the Texels have been exported to many different countries with different climate conditions such as Denmark, Egypt, Mexico, New Zealand, Poland, South Africa, Spain and finally Australia in 1993 (Keynes, 1994, Keynes, 1997, McMaster, 1994). In 1985, the Meat Animal Research Center at Clay Center, NE was the first entity to import the Texels to the United States. The Texels suitable for New Zealand and Australian conditions were selected from Denmark and Finland based on their characters such as their natural attributes of extraordinary muscling, leanness and capabilities of traveling distances. In 1988, in New Zealand, a selected Australian stock undergone quarantine and the genetic selection program was implemented. The first Australian Texels were born in 1993 and the first annual flock register was produced in April 1994 (Mason, 1996, Onan, 2000).

The inheritance of double muscling in Belgian Blue cattle has been determined as a monogenic autosomal segregation pattern (Hanset and Michaux, 1985, Charlier et al., 1995). The muscular hypertrophy (mh) locus has been named as "partially recessive" due to the fact that a single copy of the allele can have some effect, however the full double-muscled phenotype needs the sheep to be homozygous (Clop et al., 2006; Hadjipavlou et al., 2008).

Myostatin Protein

Myostatin actively inhibits skeletal muscle development (Bellinge et al., 2005). *Myostatin* is a member of the transforming growth factor (TGF)-β superfamily and can not be classified into the existing TGF-β subfamilies, such as the inhibins or the bone morphogenic proteins (Bellinge et al., 2005). This deviation from the typical TGF-β family is particularly evident in the C-terminal region (McPherron et al., 1997).

Myostatin Like other members of the transforming growth factor-β (TGF-β) family, is synthesized by a 376 amino acid precursor protein including three domains namely, a C-terminal domain or the active molecule, an N-terminal propeptide domain which will be cleaved at the RSRR site during maturation, and a signal sequence (McPherron et al., 1997) (Figure 2). Proteasic digestion processing between the propeptide domain and the C-terminal domain results in an N-terminal propeptide and the mature form of *myostatin*, a 12-kDa carboxy-terminal fragment. Both mature and unprocessed *myostatin* form disulfide-linked dimmers. Moreover, the only active form of the protein is represented the processed *myostatin* dimer (Joulia-Ekaza and Cabello, 2006).

In mice, *myostatin* is predominantly present in both developing muscle, (even as early as 9.5 days postcoitum), and adult skeletal muscle (McPherron et al., 1997). Although, there are several reports of various animal species having the occurrence of *myostatin* mRNA or protein in other tissues and in plasma as well (Gonzalez-Cadavid et al., 1998, Ji et al., 1998).

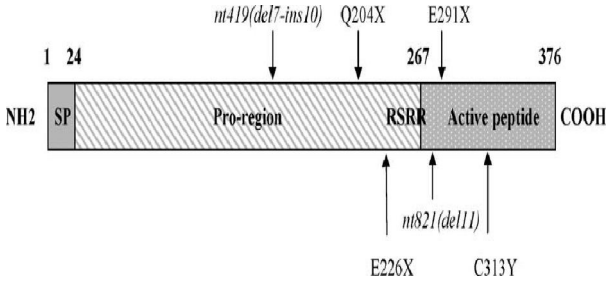

Figure 2. *Myostatin* protein structure and naturalmutations in the bovine *myostatin* gene. The three domains are the active peptide at the C-terminal part, the pro-region and the signal peptide (SP). The arrows show the position of mutations that are responsible for the increased muscle growth in some cattle breeds (McPherron et al., 1997).

The _myostatin_ pathway

While *myostatin* is bound to follistatin-related gene (FLRG), growth and differentiation factor-associated serum protein-1 (GASP-1), human small glutamin-rich tetratricopeptide repeat-containing protein Reproduced with permission of (hSGT), T-cap, follistatin or the *myostatin* propeptide then it can be found in serum or it is in an inactive state locally. The active *myostatin* dimer attaches to the activine type II receptor (ActRIIB), which then activates the type I receptor (ALK4 or ALK5) by transphosphorylation. Smad2 and Smad3 are activated as a result of the previous process. Then, Smad4 joins them. Finally, they translocate to the nucleus activating target gene transcription. Two inhibitors of this signalisation namely Smad7 and Smurf1 have been determined. Smad7 prevents *myostatin* signal by binding of its MH2 domain to the activated receptors, thus inhibiting recruitment and activation of R-Smads. Smurf1 is an E3 ubiquitin ligase that mediates ubiquitination and consequent degradation of the R-Smads (For review see Joulia-Ekaza and Cabello, 2006) (Figure 3). Expression of Smad7 is induced by the *myostatin* expression. This could express the existence of a negative regulatory feedback loop mechanism (Zhu et al., 2004).

In vitro studies show that *myostatin* causes C2C12 myoblasts to be accumulated in the G0/G1 and G2 cell-cycle phases, consequently diminishing the number of S-phase cells. Moreover, *myostatin* causes failure in myoblast differentiation which is related to a strong decrease in the expression of differentiation markers (Joulia-Ekaza and Cabello, 2006). Furthermore, under both proliferation and differentiation conditions, *myostatin* expression diminishes the apoptotic rate of cells (Thomas et al., 2000, Joulia et al., 2003). Using antisense *myostatin* mRNA, the opposite results were obtained by preventing endogenous *myostatin* expression. This approach highlighted that myogenin and p21 cyclin-dependent kinase inhibitors are probably the main physiological targets of *myostatin* (Joulia et al., 2003).

Overall, muscle hyperplasia in double-muscled Texel sheep could be explained by the above mentioned observations, and indicates that cell growth inhibition by *myostatin* is not a consequence of apoptosis rather under *myostatin* influence, myoblasts is accumulated in the G0/G1 cell cycle phases and stop growing (Thomas et al., 2000, Joulia et al., 2003, Langley, 2002).

Physiological assess of double muscling

Since the identification of double-muscled animals in the 1880s, breeders have been puzzled to explain the condition (Gan et al., 2008). Increase in muscle fiber number and in some circumstances increase in its size results in the double-muscled condition (Arthur, 1995, Boccard, 1981). The relative numbers of fast twitch glycolytic fibers are also increased due to these changes (Holmes, 1972). Growth and differentiation factor 8 (GDF8 or *myostatin*) gene directly affects muscular hypertrophy and carcass conformation (Kijas et al., 2007). It is worth noting that the mutation for muscle hypertrophy (mh) is located in the *myostatin* (MSTN) or growth and differentiation factor 8 (GDF8) gene highly conserved across species and expressed in developing and mature skeletal muscle (McPherron et al., 1997).

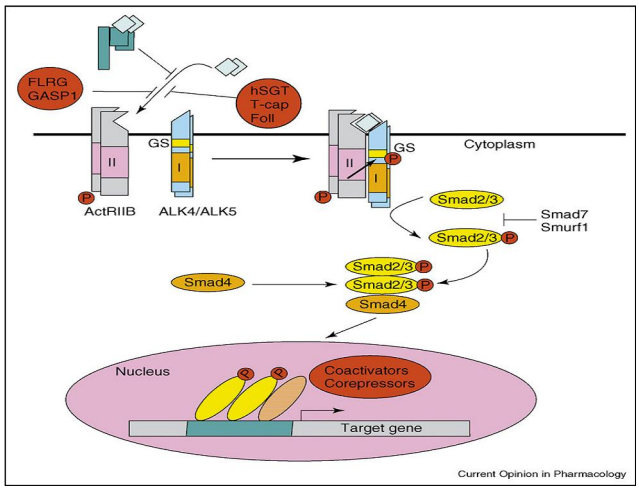

Figure 3. Famous elements of the *myostatin* pathway. (Joulia-Ekaza and Cabello, 2006).

Natural *myostatin* mutations in sheep

The new genetics science helped to reveal the genetic elements of the double muscling. The *myostatin* gene is a member of the transforming growth factor-β superfamily of growth and differentiation factors and the gene targeting in the mice was the first ignition to reveal the *myostatin* function (McPherron et al., 1997). Both skeletal muscle fibre number (hyperplasia) and mass (hypertrophy) increase revealed a negative regulator of muscle growth named as GDF8. Subsequently, the GDF8 mutations in two double muscled cattle breeds Belgian Blue and Piedmontese were identified (Grobet et al., 1997, Kambadur et al., 1997). Further study on double muscled cattle breeds revealed a series of function alleles along with allelic heterogeneity (Grobet et al., 1998). In 17 Chinese indigenous goat breeds, four haplotypes in the intron 2 of the *myostatin* gene were identified (Li et al., 2006a), and body weight were associated with *myostatin* genotypes (Li et al., 2006b).

Major genes of sheep muscle and fat composition are located either on the ovine chromosome 18 region (OAR18) including the Callipyge (Cockett et al., 1994) and rib-eye muscling (REM or Carwell) loci (Nicoll et al., 1998), or on the OAR2 region including the growth differentiation factor 8 (GDF8) also known as the *myostatin* (MSTN) gene. Recall that GDF8 is responsible for double muscling in cattle breeds (Kambadur et al., 1997, McPherron and Lee, 1997, Wiener et al., 2002). Quantitative trait loci (QTL) studies shows that a portion of the OAR2 that encompasses GDF8 has a major effect on the muscular growth in the Belgian Texel (Marcq et al., 2002), on the muscling and fat depth in the New Zealand Texel sires (Broad et al., 2000, Johnson et al., 2005), UK Texel (Walling et al., 2004) and Charollais (McRae et al., 2005) sheep. The strongest association of muscling and fatness traits of the New Zealand Texels was found in the leg (Johnson et al., 2005). This result is consistent with a QTL segregating from the Belgian Texel investigated using F2 and backcross lambs created using Romanov ewes (Laville et al., 2004).

Although, a connection of *myostatin* diversity with double-muscling is not that clear. The sequencing of the whole coding region (CDS) of the *myostatin* gene in the Texel double-muscling sheep was obtained (Marcq et al., 1998), yet were any sequence differences between the GDF8 coding sequence of double-muscled Belgian Texels and normally muscled Romanov controls found (Marcq et al., 2002). This results in the fact that the functional polymorphism resides either in a closely linked gene or inside the GDF8 non-coding region (Hadjipavlou et al., 2008).

Nowadays, the genetic structure of GDF8 effects on muscle development of the Texel sheep has been cleared. Investigations of a 10.5 kb gDNA region including GDF8 (DQ530260) tend to the identification of two biallelic SNPs. These two SNPs have significantly different allelic frequencies between hyper-muscled Texel and control animals (Clop et al., 2006). The first SNP (g.-2449G>C) was located 2.5 kb upstream from the GDF8 transcription start site. The second SNP (g.+6223G>A) has been in the 3'UTR of GDF8. Mutation(s) in the *myostatin* 3'UTR at the molecular level have been identified by Clop et al. (2006). It has been discovered that the g.+6223A allele create an illegitimate miRNA binding site that can affect the double muscling trait of the Texel sheep. This, in turn, prevent the miRNA-mediated translational of GDF8 causing double-muscling phenotype (Clop et al., 2006). Therefore, the GDF8 g.+6223A allele seems to be a causative variable of increasing muscularity in the Texel rams and could be identified as a quantitative trait nucleotide (QTN) (Hadjipavlou et al., 2008). It can be inferred from the studies that removal of GDF8's inhibitory role in sheep tends to muscle increase as it was seen in other mammalian species; therefore it is a candidate gene in growth and carcass traits studies.

Identification of double muscling in sheep

In the past, DM identification in sheep was based on the morphological characteristics such as appearance of intermuscular grooves, pelvic inclination (Bellinge et al., 2005), but now after the *myostatin* gene characterization by McPherron et al. (1997), and after the determination of mutant mh in cattle (Grobet et al., 1997), the identification is almost totally achieved via genetic marker testing. Genetic marker testing or the candidate gene approach assumes that a gene involved in the physiology of the trait could harbour a mutation causing variation in that trait for example *myostatin* for double muscling.

As previously mentioned, the GDF8 allele of the Texel sheep is characterized by one G to A transition in the 3'UTR region of *myostatin* causing double-muscling. Our review validated for g.+6223G>A SNP to be a QTN for sheep muscularity based on the strategy mentioned by Ron and Weller (2007), as previously proposed by Clop et al. (2006). Clop et al. (2006) used the PCR–restriction fragment length polymorphism analysis to test the presence of the g.+6223A QTN in Texel sheep. It seems that PCR-RFLP or genotyping method could be good options for the double muscling and muscularity identification in sheep.

Conclusions

Growth and differentiation factor 8 (GDF8 or *myostatin*) gene directly affects muscular hypertrophy and carcass conformation (Kijas et al., 2007) and double muscled Texel sheep. The GDF8 allele of the Texel sheep is identified by one G to A transition in the 3'UTR makes the gene inactive and thus, this SNP can be used as a marker to identify the double-muscled phenotype in sheep. Therefore, the GDF8 g.+6223A allele seems to be a causative variable of increasing muscularity in the Texel rams and could be identified as a quantitative trait nucleotide (QTN) (Clop et al., 2006, Hadjipavlou et al., 2008). Detection of this phenotype could be based on the PCR-RFLP analysis and RFLP markers for this trait could be the best marker for genetic marker testing.

Detection of quantitative trait nucleotide (QTN) opens the possibility of using marker assisted selection to increase genetic gain. The genetic gain rate for the double-muscling trait depends not only on the allelic frequency but also on the proportion of

homozygote animals for the A allele in the population due to the partially recessive action of *myostatin* on muscle phenotype. As a Consequence, marker-assisted selection (MAS) for this SNP could be of substantial benefit. In fact, our review indicates that marker-assisted selection (MAS) using this GDF8 SNP would be beneficial for some breeds such as the Texel and Charollais breeds and may not beneficial for some Iranian breeds such as Shal, Zel and Zandi breeds (Hadjipavlou et al., 2008, Miar et al., 2011; Mirhoseini and Zare, 2012).

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