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A Review on the Genetic Basis of Growth and Prolificacy Traits in Sheep

Abiye Shenkut Abebe1* and Mengistie Taye2

1Department of Animal Science, Debre Tabor University, P.O.Box 272, Ethiopia
2Department of Animal Production and Technology, Bahir Dar University, P.O.Box, 5501, Ethiopia

ABSTRACT

The performance of an animal for a particular trait is the result of its genetic merit and the effects of the environment where it exists. To set up genetic improvement in sheep, the genetic component attributed to the trait of interest need to be defined. The aim of this review was to describe major candidate genes influencing growth traits and prolificacy in sheep. Although growth and prolificacy are quantitative traits and are expected to be influenced by many genes with individual genes contributing small effects, there are major genes that have been identified with significant influence on growth and prolificacy. The CLPG, GDF8 and CAST genes are some of the major genes that have strong influence on sheep growth and carcass quality. The CLPG mutation can cause pronounced effect in the muscle found in the hindquarter and is responsible for the muscular hypertrophy phenotype in sheep. The GDF8 gene also play important role in increasing muscle depth due to mutation in the regulatory region and coding sequences. The CAST gene is an endogenous and specific inhibitor of calpain enzyme and thereby regulates the rate and extent of muscle tenderization following slaughtering. For prolificacy, BMP15, GDF9 and BMPR1B have been shown to exert significant influence on ovulation rate and litter size in various sheep breeds in the world. Both of the three genes are member of the TGF-beta family protein that encode protein product responsible for growth, differentiation and proliferation of ovarian follicles. The mechanism of action for such major genes are associated with the existence of mutation in the coding sequence resulting amino acid change as well as in the regulatory region that vary the expression level and inheritance of the genes. Up to now, better attempts have been made to describe the genetic basis of growth and prolificacy in sheep. However, more works are needed to characterize other genes influencing these traits. More importantly, making use of the identified genes in sheep breeding program through marker assisted and genomic selection should receive due attentions.

Keywords: Booroola gene, Callipyge gene, Growth trait, Myostatin gene, Sheep prolificacy

***Correspondence to Author:**
Abiye Shenkut Abebe
Department of Animal Science, Debre Tabor University, P.O.Box 272, Ethiopia

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1. Introduction

In a more comprehensive expression, the performance of an animal is known to be the result of its genotypic values and the environmental effects (Falconer, 1989). The genotypic values are attributed both for additive and non-additive genetic effects while the environmental aspects correspond to all effects having non-genetic origins. Sheep genetic improvement through selection requires quantifying the amount of additive genetic value or gene effects that can be inherited from parent to offspring. Although most economically important quantitative traits are governed by more number of genes including large environmental effects, there are major genes with significantly large effects on various traits. For example, mutation in Boorolla gene (FecB) is known to associate with higher prolificacy in sheep (Souza *et al*., 2001) while mutation that segregate with Callipyge (CLPG) gene causes postnatal muscular hypertrophy (Freking *et al*., 2002). While designing a breeding program, taking into consideration of the effects of such genes is essential for obtaining optimal genetic gain on the traits of interest.

Given the recent advances in molecular genetics and bioinformatics, several efforts have been made to identify the genetic basis of economically important traits (Zhang *et al*., 2016). An example of such efforts is the mapping of quantitative trait loci (QTL) in different farm animals. The QTL are genomic regions that associate with variations in phenotype. To date, about 2325 QTL have been reported in sheep QTL databases (Zhi-Liang *et al*., 2016, 2019). From the total QTL identified so far, about 341 are reported to associate with various growth traits while 137 of the QTL are known to influence reproduction traits in sheep. However, not all QTL are well characterized implying that only few casual mutations influencing growth and prolificacy have been identified. Furthermore, investigating and reporting of genes having significant effects have been usually done at individual gene level implying the need to explore the different candidate genes for a wider insight.

Knowledge on major genes having larger genetic effects on the trait of interest is important to use the genetic information in selection program (Nanekarania and Goodarzia, 2014; Gholizadeh *et al*., 2015). In sheep, growth and prolificacy are economically important traits that can significantly influence sheep breeding program (Abdoli *et al*., 213; Othman *et al*., 2016). Thus, understanding the genetics basis of these traits could play vital roles to implement genetic improvement strategies such as marker assisted selection, marker assisted introgression and genomic selection. Given the recent development in molecular techniques and reduction in the associated costs, direct selection for the genes effect is expected to be applied widely. As such, this review aimed at describing major candidate genes influencing growth and prolificacy traits in sheep.

2. Major genes influencing growth traits in sheep

In this review, growth trait represents weight at different ages, average daily weight gain and linear measurements such as body length, chest girth and height at wither. Growth traits are quantitative traits influenced by multiple genes either each gene with small effects or few genes with large effects (Falconer, 1989). Besides the involvement of more number of genes, environmental effects such as feed, health and other management practices have profound effects on quantitative traits. The focus of this review, however, was to address the genetic component of growth traits, particularly genes with major effects.

2.1. Callipyge gene

Callipyge gene, located in the telomeric region of ovine chromosome 18, is a muscular hypertrophy phenotype in sheep observed due to a single base change mutation (A to G transition) that segregate perfectly with CLPG allele (Cockett *et al*., 1994; Freking *et al*., 2002). The CLPG gene was mapped to a chromosomal

region of about 400 kb, where imprinted gene cluster containing several paternally expressed protein coding genes have been reported (Charlier *et al*., 2001; Cockertt *et al*., 2005). Interestingly, CLPG mutation has been found to be effective only if existed in heterozygous state and inherited paternally. However, sheep with homozygous genotype for CLPG mutation as well as maternal inheritance of the mutation could not yield CLPG phenotype (Cockertt *et al*., 2005). Such novel mode of inheritance is known as polar over-dominance.

The effect of CLPG mutation is pronounced in the muscle found in the hindquarter and the muscular hypertrophy phenotype is gradually expressed after about 3weeks of age (Cockett *et al*., 1997). Such functional characteristics of CLPG mutation is essential to minimize the risk of dystocia during lambing. Furthermore, Callipyge lambs are known to display valuable production and meat quality characteristics such as higher dressing percentage and larger longissimus (loin eye) region with preferable lean composition as compared to normal muscled lambs (Cockett *et al*., 2005). In addition, CLPG mutation can improve feed conversion efficiency and lower daily feed intake (Jackson *et al*., 1997), which is an advantage for large scale breeding of Callipyge lambs as it could potentially reduce feed cost.

Although the CLPG mutation is very important for increased muscle weight, it has some negative effects such as relatively low fleece weight and less carcass tenderness in Callipyge lamb as compared to the normal phenotype (Jackson *et al*., 1997). Such undesirable effects, however, are not believed to outweigh the positive contribution of CLPG mutation. The CLPG mutation was first reported in American Dorset sheep breed (Cockett *et al*., 1997). The Callipyge phenotype has been also reported in Rambouillet and Hampshire sheep (Jackson et a., 1997) and searching for the mutation in other breeds has been continuing (Quanbari *et al*., 2007; Gabor *et al*., 2009; Nanekarania and Goodarzia, 2014). The nature of the CLPG mutation is an important characteristics for marker assisted introgression to increase growth trait in sheep.

2.2. Myostatin gene

Myostatin gene, also known as growth differentiation factor 8 (GDF8), is a member of the TGF-beta (transforming growth factor-beta) protein family and encodes protein that negatively regulates muscle proliferation and differentiation (Marcq *et al*., 1998). This gene is located on ovine chromosome 2. Mutation in Myostatin gene that results in loss of function is already known to cause double muscling in cattle (Kambadur *et al*., 1998; Wiener *et al*., 2002). In sheep, Johnson *et al*. (2005) reported a QTL close to GDF8 gene with significant effect on muscle development. Moreover, Hadjipavlou *et al*. (2008) reported two single nucleotide polymorphisms in GDF8 gene that significantly associate with muscle depth in commercial Charollais sheep. Thus, genetic selection and introgression could provide excellent opportunities to improve sheep muscling by making use of mutations in GDF8 gene.

2.3. Calpastatin gene

Calpastatin (CAST) gene, mapped on ovine chromosome 5, is the endogenous and specific inhibitor of Calpain enzyme and thereby regulates the rate and extent of muscle tenderization following slaughtering of animals (Hopkins and Taylor, 2004; Casas *et al*., 2006; Azari *et al*., 2012). Calpain is a protein belonging to the family of calcium-dependent proteolytic enzyme that degrades the muscle structure in mammals, particularly the myofibrillar protein muscle (Hopkins and Taylor, 2004). This enzyme has different structural components that require varied level of calcium ion for enzymatic activation. The CAST gene interferes the activity of the calpain enzyme by binding the calcium ion with structural components of the enzyme making the ion an available for use. Thus, genetic variations within the CAST gene are assumed to affect the gene's inhibitory role. Different genetic variants have been reported in both the coding and non-coding regions of ovine

CAST gene (Zhou *et al*., 2007; Chung and Davis, 2012; Mohsen *et al*., 2014).

Thus far, significant associations between CAST gene variant and meat tenderness have been reported in beef cattle (Casas *et al*., 2006; Schenkel *et al*., 2006) and in pig (Ciobanu *et al*., 2004). In sheep, Byun *et al*. (2008) reported significant effect of CAST gene variant on lamb birth weight while Chung and Davis (2012) identified significant association with birth weight and average daily gain, revealing the possible involvement of this gene in muscle growth. Majority of the study on ovine CAST gene focused on investigating the level of polymorphism in different sheep population, which is indeed the starting point for further investigation. The presence of CAST gene polymorphism has been investigated in several sheep breeds. For instance, in Turkish sheep breeds (Yilmanz *et al*., 2014), Afshari sheep in Iran (Nikmard *et al*., 2012), Arabic sheep (Mohammadi *et al*., 2008) and in Lori sheep (Nanekarania and Goodarzia, 2014).

2.4. Other genes influencing growth in sheep

Several candidate genes influencing growth traits in sheep have been reported (Walling *et al*., 2002; Forutan *et al*., 2016; Zhang *et al*., 2016; Pasandideh *et al*., 2018). However, more efforts are needed to identify the casual mutations. Identifying the casual mutation is very important to design genetic improvement targeting a specific trait influenced by the mutation using marker assisted introgression. A typical example is the rib-eye muscle (REM) locus mapped to ovine chromosome 18 near to CLPG map position. Unlike CLPG, the effect of REM is only on longissimus muscle (rib-eye area), with no effect on hindquarter or live weight and back fat thickness (McEwan *et al*., 1998).

3. Major genes influencing prolificacy in sheep

Prolificacy in sheep can be described as the number of lambs born per ewe per lambing. It is one of the economically important reproductive traits in sheep. Prolificacy is closely linked with ovulation rate implying that as more ova shed from the ovary, the possibility of having more number of lambs will be high. Mutations influencing prolificacy of sheep have been reported at different loci in the genome (Abdoli *et al*., 2016, 2018; Talebi *et al*., 2018). Some of the major genes influencing prolificacy in sheep are discussed below.

3.1. Bone Morphogenetic Protein 15

Bone Morphogenetic Protein 15 (BMP15) gene was mapped on ovine chromosome X and known to influence the prolificacy of sheep. The BMP15 gene, expressed in the oocyte, is a member of the TGF-beta family whose protein products play crucial roles in folliculogenesis (Demars *et al*., 2013). It is clear that the number of matured ovarian follicles is fundamental to get more number of offspring. So far, multiple mutations on BMP15 gene that can contribute for higher prolificacy were identified in various sheep breeds (Bodin *et al*., 2007; Abdoli *et al*., 2016; Amini *et al*., 2018). For example, Amini *et al*. (2018) reported that a single (c.755T>C) nucleotide change on exon two of BMP15 gene has shown significant association with litter size in four Iranian sheep breeds. Similarly, Bodin *et al*. (2007) found a missense mutation that cause a transition of cysteine to tyrosine amino acid on the 53 codon, which consequently lead to an increase of ovulation rate in Lacaune sheep breed.

In different sheep populations, the heterozygote carriers for BMP15 mutations are reported to have an increased ovulation rate and litter size compared to the wild-type alleles (Davis *et al*., 2006; Bodin *et al*., 2007; Amini *et al*., 2018). The homozygote genotypes for the mutations, on the other hand, are known to be sterile owning to dosage effect of the gene that could cause hypertrophy in the ovary. The exceptions reported so far are the nucleotide changes at g.1009A>C in Olkuska (Poland) and at g.950C>T in Givette (France) sheep breeds, where homozygous ewes for the two mutations in BMP15 gene are unexpectedly hyper-prolific

(Demars *et al*., 2013). Given the availability of multiple mutations associated with ovulation rate and litter size, BMP15 gene could provide better opportunities to exploit the potential of prolific sheep using the state of art technologies in animal breeding.

3.2. Growth Differentiation Factor 9

The growth differentiation factor 9 (GDF9) gene is located on the ovine chromosome 5 and known to display autosomal over-dominant inheritance pattern (Nanekarani *et al*., 2016). Functionally, it has been shown to be very important for primordial follicle growth and stimulates granulosa cell proliferation (Abdoli *et al*., 2016). Different mutations showing significant influence on ovulation rate and litter size have been distinguished in various sheep populations around the world. For instance, Våge *et al*. (2013) identified a missense mutation in the bioactive part of the GDF9 protein showing strong association with litter size in the Norwegian white sheep breed. Furthermore, Hanrahan *et al*. (2004) reported eight mutation at different position on the GDF9 gene of Cambridge and Belclare sheep although only five of them alter amino acid sequence.

The GDF9 shares similar characteristics with BMP15 gene in that ovulation rate and litter size have been known to be increased in ewes carrying the heterozygous mutant allele while becoming sterile when the two mutant alleles appeared together (Hanrahan *et al*., 2004; Våge *et al*., 2013). Both genes are member of the TGF-beta family protein that play vital roles in the regulation of cellular processes such as growth, development, proliferation and embryogenesis. Because of such functional characteristics, the GDF9 gene is known to contribute a lot for an increased prolificacy in sheep.

3.3. Bone Morphogenetic Protein Receptor 1B

The bone morphogenetic protein receptor 1B (BMPR1B) also known as Booroola gene (FecB) or activin-like kinase 6 (ALK6) was the first major gene identified influencing prolificacy in sheep (Souza *et al*., 2001). The gene has been mapped to ovine chromosome 6 and known to follow autosomal dominant inheritance pattern. The FecB gene is expressed in the oocyte and granulosa cell within the ovary including other tissues such as in the pituitary gland where secretion of hormones regulating the activity of ovary takes place (Montgomery *et al*., 2001). The FecB mutation in sheep is attributed to a single nucleotide change (A to G) at the 746th position of the coding sequence that resulted in substitution of glutamine with an arginine (Souza *et al*., 2001). Such amino acid change has been observed in the highly conserved intracellular kinase signaling domain of the gene.

The change in amino acid could cause functional change in the intracellular kinase domain of mature protein that result in development of large number of small antral follicles resulting in increased ovulation rate. The gene dosage effect of the FecB mutation is additive for the ovulation rate with an increase of 1.5 for each gene copy that subsequently contribute for increased liter size (Dincel *et al*., 2015). The presence of FecB mutation affecting ovulation rate and litter size was first identified in Merino sheep but later reported in other sheep such as Belclare, Cambridge, China Small Tailed Han, Romney, Kendrapada, Garole and Javanese sheep (Dincel *et al*., 2015). Due to its contribution for high prolificacy, FecB gene has received significant attention in sheep breeding program of various countries.

4. Conclusion

This review aimed at exploring major genes influencing growth traits and prolificacy in sheep. Although growth and prolificacy are quantitative traits and are expected to be influenced by many genes with individual genes contributing small effects, there are major genes that have been identified with significant influence on growth and prolificacy. In connection to this, CLPG, GDF8 and CAST genes are some of the major genes that have strong influence on sheep growth and carcass quality. For prolificacy, a

number of genes have been identified but BMP15, GDF9 and BMPR1B have been shown to exert significant influence on ovulation rate and litter size in various sheep breeds in the world. The mechanism of action for such major genes are associated with the existence of mutation in the coding sequence resulting amino acid change as well as in the regulatory region that vary the expression level and inheritance of the genes. Up to now, better attempts have been made to describe the genetic basis of growth and prolificacy in sheep. However, more works are needed to characterize other genes influencing these traits. More importantly, making use of the identified genes in sheep breeding program through marker assisted and genomic selection should receive due attentions.

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