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# Candidate Genes Associated with Economically Important Traits of Sheep - A Review

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## Summary

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Sheep give meat, milk, wool to the human population and this makes them a significant part of the world livestock industry. The basis of meat, milk and wool production is reproduction, respectively the success of reproduction. The result of reproduction is under the direct influence of genotypes and external factors and their interaction. The most important sheep product is meat and it is the main reason why sheep are raised in most countries. Milk is an important product of sheep, it is the basic food of young lambs and it plays an important role in the diet of the population. Wool makes sheep unique and therefore they are recognizable at first sight, in other words, different from other types of animals. Wool is a characteristic product of different and very variable economic importance, in some countries it is the most important product of sheep which provides the largest part of income. Many genes correlated with diverse economically significant phenotypic characteristics and their roles have been reported in domestic animals to date. In animal breeding, the identification of candidate genes correlated with economically important traits of sheep is crucial. The detailed information of the classified genes connected with significant traits helps to improve production capacity and productivity of sheep. Moreover, in this way the sheep processing industry can be increased, and thus the profitability and benefit of sheep breeders. The aim of this review is to provide complete information on the identified candidate genes associated with important production traits of sheep.

## Key words

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sheep, meat, milk, wool, candidate genes

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## Introduction

10,000 years ago, in the area of the Fertile Crescent, one of the earliest domesticated animal species were sheep. After domestication, a wide diversity of sheep breeds developed during the spreading to other regions (Larson et al., 2014; Lv et al., 2015; Gorkhali et al., 2016; Xu and Li, 2017). Sheep give meat, milk, wool to the human population and this makes them a significant part of the world livestock industry (Safari et al., 2005; Xu and Li, 2017). According to Martínez et al. (2016), the genomic region accountable for the variation of a quantitative characteristic is QTL. Also there is a genome-wide association study (GWAS). According to Zhang et al. (2012), the genome-wide association study (GWAS) is essential to identify candidate genes for many quantitative traits. To date, in domestic animals, many genes correlated with diverse economically significant phenotypic characteristics, and their roles have been reported. The aim of this review is to provide complete information on the identified candidate genes associated with important production traits of sheep.

## Methodology

During literature analysis, about one hundred references were screened and the 69 were selected as the most appropriate for the realisation of the paper goal. In the search, key search terms were: candidate genes; milk, wool, and meat sheep production; economically important traits in sheep. Relevance and recentness were set as selection criteria for inclusion or exclusion of studies.

## Genes Correlated with Fertility Traits

The basis of meat, milk and wool production is reproduction, respectively the success of reproduction. The result of reproduction is under the direct influence of genotypes and external factors and their interaction (Mioč et al., 2007). Fertility traits like ovulation rate, litter size, total number of lambs born, age at first lambing, age at first puberty and stillbirth have a great influence on the economy of the sheep industry. Ovulation rate and litter size are the most significant characteristics and also have high economic worth (Chen et al., 2015; Gebreselassie et al., 2020). Various genes control fertility as well as fecundity features with diverse influences on sheep (Drouilhet et al., 2009; Gebreselassie et al., 2020). Genes associated with ovulation rate, litter size, and sterility of sheep breeds have been identified by the GWAS study. These are the genes: growth differentiation factor 9 (GDF9), bone morphogenetic protein receptor IB (BMPRII) and bone morphogenetic protein 15 (BMP15) (Galloway et al., 2000; Souza et al., 2001; Hanrahan et al., 2004; Gebreselassie et al., 2020). Ovulation level and litter size are affected by BMPRII, while BMP15 along with GDF9 play an important role in follicle formation. The GDF9 gene is a protein belonging to the TGF- $\beta$  family and it additionally controls the development of the ovarian follicle. On the other hand, granulosa cells, theca cells and oocytes are affected by BMP15 (Davis et al., 1982; Yan et al., 2001; McNatty et al., 2005; Gebreselassie et al., 2020). In addition to fertility traits, there are also reproductive performance traits. Studies have shown genetic variants associated with reproductive abilities in some sheep breeds. A gene correlated with sensitivity to sheep lentivirus has been identified by GWAS study and its role is to

reduce sensitivity to lentivirus (Gebreselassie et al., 2020). Genes, fertility and reproductive traits and sheep breeds are shown in Table 1.

**Table 1.** Candidate genes responsible for fertility traits in sheep (Gebreselassie et al., 2020)

| Genes          | Chromosome | Traits | Sheep Breed        |
|----------------|------------|--------|--------------------|
| <i>PRLR</i>    | 16         | RP     | Herdwick & RFD     |
| <i>TMEM154</i> | 17         | ILV    | Herdwick & RFD     |
| <i>CCNB2</i>   | 7          | OD     | GMM, CMF & AWD     |
| <i>SLC8A3</i>  | 7          | OD     | GMM, CMF & AWD     |
| <i>GDF9</i>    | 5          | ORS    | Cambridge&Belclare |
| <i>BMP15</i>   | X          | ORS    | Cambridge&Belclare |
| <i>BMPRII</i>  | 6          | ORS    | Lacaune Sheep      |
| <i>BMPRII</i>  | 7          | LS     | Han sheep          |
| <i>BMP15</i>   | X          | LS     | Han sheep          |

\*RP - reproductive performance; ILV - infection to the lentivirus; OD - oocyte development; ORS - ovulation rate & sterility; LS - litter size; GMM - German mutton merino; AWD - African white dorper; RFD - Rough Fells & Dalesbred; CMF - Chinese Mongolian fat-tailed

## Genes Correlated with Meat Production Traits

The most important sheep product is meat and it is the reason why sheep are raised in most countries. Lamb is much tastier and more sought-after, therefore fattening of adult sheep is almost neglected. For example, in New Zealand, of the total annual number of slaughtered sheep of different categories, 80% are lambs (Mioč et al., 2007). Even though mutton accounts for just 6% of world meat consumption, in regions of North Africa, the Middle East, India, and parts of Europe it is the main meat. The largest consumer of lamb and the first importer of lamb is the European Union; 99% of imported lamb comes from Australia and New Zealand (FAO, 2013). The best known and most thoroughly studied QTLs in sheep have been associated with muscle hypertrophy. The most described callipyge phenotype is connected with postnatal hypertrophy of muscle tissue with the concurrent decrease of carcass fatness (Cockett et al., 1996; Cockett et al., 2005; Knapik et al., 2017). The major gene that significantly influences carcass composition is Callipyge gene. In some sheep populations, a mutated variant of the normal (*clpg*) gene is located on the distal part of chromosome 18. Lower daily feed intake (Jackson et al., 1997; Knapik et al., 2017), better food efficiency and better slaughter quality are characteristics of Callipyge lambs, compared to lambs without this specified gene. This gene was originally identified in the herd of American Dorset and is inherited dominantly. Increased hardness of some muscles (Koochmarai et al., 1995; Shackelford et al., 1997; Knapik et al., 2017) is one of the worst effects of the Callipyge gene (Mioč, 2020). The Callipyge gene was first observed in the United States in 1983. Animals with the Callipyge phenotype have an increased muscle mass of 30%, particularly in the hindquarter. When

lambs of both sexes are about a month old, this phenomenon occurs and results in a higher proportion and a larger diameter of fast-twitching muscle fibers (Jackson et al., 1997; Reflexions, 2016; Knapik et al., 2017). Callipyge phenomenon is interesting to geneticists because of one very peculiar particularity: unique mode of heredity transmission (Reflexions, 2016). According to Cockett et al., 1996 and Knapik et al., 2017, only in heterozygous offspring that inherit the CLPG mutation from their fathers is the callipyge mutation phenotypically displayed. This unique mode of inheritance is called polar overdominance.

Another gene related to meat tenderness and growth performance characteristics in sheep is Calpain (CAPN) gene (Mahrous et al., 2016; Arora et al., 2019; Kumar et al. 2015). In Chall and Zel sheep breeds, meat quality and fatty acid composition are influenced by genetic variants that have been recognized in the calpastatin (CAST) gene (Aali et al., 2017; Gebreselassie et al., 2020). Also a gene that affects tenderness and rib eye (loin) muscling is the Carwell gene (Nicoll et al., 1998; Jopson et al., 2001; Warner et al., 2010). Myostatin actively inhibits the development of skeletal muscle (Bellinge et al., 2005), and is also identified by reducing in total lean meat and increasing of the proportion of loin meat (Hickford et al., 2010; Gebreselassie et al., 2020). Genes for meat production traits and sheep breeds are shown in Table 2.

## Genes Correlated with Milk Traits

Milk is an important product of sheep, it is the basic food of young lambs and it plays an important role in the diet of the entire population. Sheep's milk is most often consumed in the form of cheese (Mioč et al., 2007). An important part in the agricultural economies of many countries, especially in the Mediterranean and Middle East regions, is covered by dairy sheep industry (Selvaggi et al., 2014; Suárez-Vega et al., 2016). Prolactin (PRL), leptin (LEP), insulin-like growth factor hormone 1 (IGF1), diacylglycerol O-acyltransferase 1 (DGAT1), signal transducer and activator of transcription 5 (STAT5), alpha ( $\alpha$ )s2-casein (CSN1S2), growth hormone receptor (GHR), and growth hormone-releasing hormone receptor (GHRHR) are very important candidate genes connected with milk and growth traits (Moioli et al., 2007; Orford et al., 2010; Staiger et al., 2010). Prolactin is crucial for lactation and has a significant function in milk production (Knight, 2001), while leptin has a significant part in animal growth and metabolism (Choudhary et al., 2005). IGF1 gene affects the litter size and the persistence of lactation (Scatà et al., 2010; He et al., 2012; Luridiana et al., 2020). DGAT1 is perhaps connected with variation in milk fat content (Kumar et al., 2016), and has a significant part in triacylglycerol biosynthesis, likewise in milk and growth traits (Chen et al., 2002; Abousoliman et al., 2020).

**Table 2.** Candidate genes responsible for meat production traits in sheep (Knapik et al., 2017)

| Gene symbol          | Gene name                                 | Traits  | Breed   |
|----------------------|---|---|---|
| <i>CLPG</i>          | Callipyge                                 | MH, CF; Impact on FE and DFI  | American Dorset   |
| <i>Carwell locus</i> | The rib-eye muscling locus (REM), Carwell | MH – <i>longissimus dorsi</i> muscle; increases the rib-eye area – about 11% and weight of the <i>longissimus dorsi</i> muscle – about 7% | Australian Poll Dorset  |
| <i>MSTN (GDF8)</i>   | Myostatin                                 | Increases muscularity; Effect MC and FC in lamb carcasses   | Belgian Texel<br>Texel sheep  |
| <i>CAST</i>          | Calpastatin                               | LWG, CW, <i>longissimus dorsi</i> shear force; Impact on daily gain birth to weaning  | Dorset Down, Dorset Down x Coopworth, Kurdi sheep, Chall Iranian sheep, Zel Iranian sheep |
| <i>FABP4</i>         | Fatty acid binding protein 4              | MT, MS, IFC in <i>longissimus dorsi</i>   | Small-Tailed Han sheep, Tan sheep, Inner Mongolia sheep                                   |
| <i>DGAT1</i>         | Diacylglycerol acyltransferase 1          | MT, IMF content and MS  | Small-Tailed Han sheep, Tan sheep, Inner Mongolia sheep                                   |
| <i>LEP</i>           | Leptin                                    | Increase of fat-tail percent, total body fat weight   | Iranian sheep breeds (Shal, Zandi, Zel)   |
| <i>TNNC2</i>         | Fast skeletal muscle troponin C           | MT, MS pH and CW  | Small-Tailed Han sheep, Tan sheep, Inner Mongolia sheep                                   |

\*MH – muscle hypertrophy; CF – carcass fatness; MC – meat content; FC – fat content; MT – meat tenderness; MS – marbling score; CW – carcass weight; FE – feed efficiency; DFI – daily feed intake; LWG – live weight gain; IFC – intramuscular fat content

STAT5 represents central role in signal transduction from prolactin to milk protein genes (Bole-Feysot et al., 1998; Abousoliman et al., 2020). Caseins represent approximately 80% of proteins in ruminant milk (Haug et al., 2007; Park et al., 2007; Balthazar et al., 2017; Abousoliman et al., 2020). Casein is composed of 4 fractions:  $\alpha$ S1-casein (6.7%),  $\alpha$ S2-casein (22.8%),  $\beta$ -casein (61.6%), and  $\kappa$ -casein (8.9%) (Selvaggi et al., 2014; Balthazar et al., 2017). The CN gene family, along with CSN1S1 and CSN1S2, is determined on bovine chromosome 6, which is correlated with milk components and milk quality (Boettcher et al., 2004; Kucerova et al., 2006; Caroli et al., 2009; Ardicli et al., 2018). A meaningful impact of the CSN1S2 locus was detected on milk protein content (Ardicli et al., 2018). GH and GHRH are important candidate genes because they control body growth and are correlated with growth success, body size, and meat quality in cattle (Waters et al., 2001; Di Stasio et al., 2005; Garrett et al., 2008; Reardon et al., 2010; Abousoliman et al., 2020). It is noticed in Turkish sheep breed that POU class 1 homeobox 1 (POU1F1) gene influences milk production (Ozmen et al., 2014; Gebreselassie et al., 2020) Furthermore, it has a major function in controlling the function of growth hormone as well as prolactin genes (Lan et al., 2009; Gebreselassie et al., 2020). Genes associated with milk traits are recognized in other sheep breeds. These genes are palmdelphin (PALMD), ring finger protein 145 (RFP145) and alpha-lactalbumin (LALBA) (García-Gómez et al., 2012; Moiola et al., 2013; Gebreselassie et al., 2020). Genes for milk and growth traits are presented in Table 3.

### Genes Correlated with Wool Traits

Wool makes sheep unique and therefore they are recognizable at first sight, in other words, different from other types of animals. Wool is a characteristic product of different and very variable economic importance, in some countries it is the most important product of sheep which provides the largest part of income. In Australia, 3/4 of sheep are raised for wool. Australia produces about a quarter of the world's unwashed wool, while Europe accounts for about 12% of total annual world wool production. (Mioč et al., 2006; Mioč et al., 2007). Fiber diameter, staple length, fineness dispersion and crimp are significant wool characteristics that define the quality of wool (Wang et al., 2014; Gebreselassie et al., 2020). Also, the focus is on fiber diameter coefficient of variation, shedding, color and hair follicles (Fu et al., 2016; Xu and Li, 2017). Genes affirmed to be correlated with sheep wool are Keratin-Associated Protein (KAP) and Follistatin (FST); in Chinese merino sheep, the FST gene, which is located on chromosome 16, was identified for wool fiber diameter and wool crimp traits (Ma et al., 2017). Wool quality is also associated with the keratin gene family (KAP6.1, KAP8.1, KAP8.2, KRTAP9-2, and KAP16.4) which controls the function of wool and the growth of hair follicles (Ma et al., 2017; Gebreselassie et al., 2020). A greatly valuable trait is coat color. Coat color helps to differentiate among breeds and varieties; for sheep breeds, it is a significant economic trait. According to Song and Li, 2017; Koseniuk et al., 2018; Gebreselassie et al., 2020, v-kit Hardy-Zuckerman 4

**Table 3.** Candidate genes responsible for milk and growth traits

| Gene symbol   | Gene name  | Chr | Traits   | Breed                         |
|---------------|--|-----|--|-------------------------------|
| <i>POU1F1</i> | POU class 1 homeobox 1                             | 1   | MY   | Turkish sheep                 |
| <i>RFP145</i> | Ring finger protein 145                            | na  | MY   | Italian Altamurana            |
| <i>LALBA</i>  | Alpha -lactalbumin                                 | 3   | MP   | Spanish Churra                |
| <i>GH</i>     | Growth hormone                                     | 11  | MT, BG<br>Lower MY                                 | All breeds<br>Serrada Estrela |
| <i>GHRH</i>   | Growth hormone-releasing hormone receptor          | 4   | BG   | All breeds                    |
| <i>PALMD</i>  | Palmdelphin  | na  | MY   | Italian Altamurana            |
| <i>PRL</i>    | Prolactin  | 20  | MY, MC   | All breeds                    |
| <i>LEP</i>    | Leptin   | 5   | AG, metabolism                                     | All breeds                    |
| <i>IGF1</i>   | Insulin-like growth factor hormone 1               | 3   | LS, LP   | All breeds                    |
| <i>DGAT1</i>  | Diacylglycerol O-acyltransferase 1                 | 9   | MFC, MT, GT  | All breeds                    |
| <i>STAT5</i>  | Signal transducer and activator of transcription 5 | 11  | Signal transduction from prolactin to milk protein | All breeds                    |
| <i>CSN1S2</i> | Alpha ( $\alpha$ )s2-casein                        | 6   | MPC  | All breeds                    |

\*Chr – Chromosome; AG – animal growth; LP – lactation persistence; LS – litter size; MY – milk yield; MP – milk production; MC – milk composition; MT – milk traits; GT – growth traits; na – not available; MFC – milk fat content; MPC – milk protein content; BG – body growth

**Table 4.** Candidate genes responsible for wool traits (Gebreselassie et al., 2020)

| Gene symbol     | Gene name                       | Chromosome | Trait | Breed                  |
|-----------------|---------------------------------|------------|-------|------------------------|
| <i>KAP6.1</i>   | Keratin associated protein 6.1  | na         | Wool  | Merino (Xinjiang type) |
| <i>KAP8.1</i>   | Keratin associated proteins 8.1 | 1          | Wool  | Merino (Xinjiang type) |
| <i>KAP8.2</i>   | Keratin associated protein 8.2  | na         | Wool  | Merino (Xinjiang type) |
| <i>KRTAP9-2</i> | Keratin associated protein 9-2  | na         | Wool  | Merino (Xinjiang type) |
| <i>KAP16.4</i>  | Keratin associated protein 16.4 | na         | Wool  | Merino (Xinjiang type) |
| <i>FST</i>      | Follistatin                     | 16         | WQ    | CMS (Junken Type)      |
| <i>MC1R</i>     | Melanocortin 1 receptor         | 14         | Color | MRA                    |
| <i>ASIP</i>     | Agouti signaling protein        | 13         | Color | Dubian & Privorianp    |

\*WQ - wool quality; na - not available; CMS - Chinese Merino Sheep; MRA - Manchega & Rasa Aragonesa

feline sarcoma viral oncogene homologue (KIT), agouti signaling protein (ASIP), microphthalmia-associated transcription factor (MITF) and the melanocortin 1 receptor (MC1R), tyrosinase-related protein 1 (TYRP1) are candidate genes responsible for coat color. Genes for wool traits are shown in Table 4.

## Conclusion

In animal breeding, the identification of candidate genes correlated with economically important traits of sheep is crucial. Many genes correlated with various phenotypic characteristics have been recorded in sheep. Certain stated genes influence more than one trait. The detailed information of the classified genes connected with significant traits helps to improve production capacity and productivity of sheep. Moreover, in this way the sheep processing industry can be increased, and thus the profitability and benefit of sheep breeders. In order to advance the effectiveness of sheep production, further research work in this field is needed.

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