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Review Article

GENETIC MARKERS ASSOCIATED WITH FECUNDITY IN SHEEP

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Abstract: Livestock and its inputs and outputs are a growing economic sector. The livelihood and income effects of the livestock economy are huge. More than a billion people in Asia keep livestock, 60% of rural households do so. It is the major income source of the poor and especially of women in developing countries. So, the main aim of any animal breeder is to get maximum profit from domestic livestock. This can be achieved by two basic tools i.e. selection and breeding. Sheep production efficiency is mainly conditioned by fertility. Some researchers also reported that number of offspring obtained per lambing is more vital than gain of weight. Due to low heritability selection for reproduction traits is usually difficult. So for these traits marker assisted selection (MAS) targeting fecundity will ultimately improve the reproduction rate and production efficiency. Number of candidate genes has been identified so far influencing fecundity. Therefore, present paper aimed to review the battery of fecundity gene in different sheep breeds.

Keywords: Fecundity, heritability, litter size, livestock, markers.

Introduction

Sheep with its multi-facet utility for wool, meat, skin and manure, form an important component of rural economy particularly in the arid, semi-arid and mountainous areas of the country. It provides a dependable source of income to the shepherds through sale of wool and animals. Sheep production has some added advantages like animals do not need expensive housing and require less labour than other kinds of livestock. The foundation stock is relatively cheap and the flock can be multiplied rapidly. Sheep rearing in India is now facing a dilemma to produce more mutton and wool for growing human population against the reality of shrinking grazing resources, creating a major constraint to further growth of sheep population. As per the 19th livestock census (2012) there is -9.07 per cent declines in sheep population in India between 2007 to 2012. The number of lambs per ewe is the main factor which contribute maximum to mutton production. Most of the Indian breeds generally single lamb per lambing.

Fertility is one of the important parameters controlling the biological efficiency of sheep in regard to meat, milk and wool production (Notter *et al*., 2000). The number of offspring

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obtained per lambing is a good indicator, and it is more important than gain of lambs (Petrovic 2000). In domestic livestock including small ruminant's improvement of reproductive efficiency has been the key interest of any animal breeders but reproductive traits are mostly sex limited and expressed in later part of life besides having low heritability value. Hence traditional selection method proved less effective for genetic improvement. Therefore, marker assisted selection can be used as an alternative choice. Incorporation of genetic markers in the selection experiment would ultimately over a period of time. Selection intensity with respect to a certain trait is relatively higher through indirect selection like candidate gene approach and thus, overall genetic progress can be improved for the desired trait at a considerably higher rate (Rupp and Boichard 2003).

Battery of candidate genes with physiological effects on reproduction traits and located in the vicinity of identified QTL for such traits are being targeted and studied for possible roles in the control of expression of varying phenotypes observed in different breeds or within breeds at different locations. High litter size or twinning is an economically important trait that enhances sheep productivity in terms of producing a higher number of lambs, meat and wool (Mishra 2014). The booroola merino was the first breed of sheep where ovulation rate and litter size were shown to be affected by a segregating major gene (Piper *et al*., 1988). Records from prolific flocks in several countries have subsequently revealed a further major gene that increases prolificacy in sheep (Table 1). Therefore, present paper aimed to review the important fecundity gene affecting prolificacy in different sheep breeds.

Importance of litter size:

Litter size has a major impact on efficiency and profitability in lamb meat production. In India sheep production is very low and known to be less profitable due to small herds and a large amount of labor spent on each ewe. Developing fertility traits may therefore be of big interest for sheep producers (Kumm 2009). Ovulation rate and litter size are important fertility traits in sheep and are of high economic value (Notter 2008). Focusing of development of fertility traits will have a long term effect on profitability in the sheep production (Pramod *et al*., 2013).

Table 1 Prolific sheep breed with average litter size

Breed	Genotype	Litter size	Reference
Garole	FecBB/FecBB	1.98	Kumar *et al* (2006)
Garole	FecBB/FecBB	1.68	Sharma *et al* (1999)
Chinese Merino	FecBB/FecBB	2.84	Guan *et al* (2007)
Romney	FecBB/FecBB	2.34	Farquhar *et al* (2006)
	FecBB/FecB+	2.44	
Deccani crossbred	FecBB/FecB+	1.36	Nimbkar *et al* (2007)
GaroleX Malpura	FecBB/FecB+	1.46	Sharma *et al* (2004)
Booroola Merino	FecBB/FecBB	2.5	Bindon (1984)
Hu	FecBB/FecBB	2.09	Liu *et al* (2003)
Small Tail Han	FecBB/FecBB	2.47	Wang *et al* (2003)

Since selection of breeding candidates is complicated it is important to study genes associated with fertility so that breeding can include genotypic information from animals. This will increase the genetic improvements in reproduction traits since it will be easier to collect data and information of the animal's traits. In most sheep production systems now a days the main objective is to maximize farm profit in lamb meat production which includes maximizing the number of lambs slaughtered and the weight and composition of the carcass. Thus, increasing litter size should be the primary goal of sheep production system.

Reproductive status and Follicles Development in Sheep:

Ovulation is a complex mechanism that differs among species and depends both on genetic and environmental factors. Mammals can be either mono or poly-ovulatory based on how many oocytes that mature and are released during ovulation. Ruminants typically releases a single oocyte per ovulation compared to pigs and rodents which have high ovulation rates (Montgomery *et al*., 2001). The ovulation rate even differs between breeds. In sheep, it ranges from one egg per ovulation in Texel and Suffolk to ten eggs per ovulation in the prolific Booroola Merino breed (Hanrahan 1984; Souza *et al*., 2001). Beside genetic background, various non genetic factors like age, season and nutrition also leads to variation in ovulation rate between animals.

Follicle development includes a series of stages classified by the number of granulosa cell layers surrounding the oocyte and depends on the presence of certain hormones (Montgomery *et al*., 2001). The development starts with the primordial phase (the primitive or non-growing phase) where the oocyte is surrounded by a single layer of epithelial cells. The follicle then develops into the primary and secondary phase where the epithelial cells proliferate into granulosa cells and theca cells separated by the basal lamina. The growth and differentiation of granulosa cells is stimulated by FSH and the proliferation of theca cells is influenced by LH. The theca cells secrete androgens that are converted into estrogen. Granulosa cells are essential for ovulation since they support the oocyte and secret the hormones estrogen and inhibin. The oocyte is also surrounded by a non-cellular material layer called the zona pellucida (Sjaastad *et al*., 2003). The oocyte starts to prepare for ovulation after being influenced by hormones (Montgomery *et al*., 2001). Estrogen stimulates preovulatory surge of lutenzing hormone (LH) which induce maturation of the follicle which then is ready to ovulate. In mono-ovulatory species like sheep, only a few selected follicles mature and become dominant (Sjaastad 2003). The stages in follicle development can also be divided into the pre-antral and antral stages which are gonadotrophin-responsive and gonadotropin-dependent respectively (Pramod *et al*., 2013).

Factors affecting litter size in sheep:

Many genetic and non genetic factors influence litter size in sheep. Several factors likes age, season, management, nutrition, genetic effect, pre and post weaning period, ovulation rate, embryo survival, lamb survival, environmental conditions, uterine capacity and milking capacity affects litter size in sheep. Fertility traits such as litter size (0.06-0.13) and ovulation rate have low heritability (Janssens *et al*., 2004). So selection based on genotype is more effective. Fecundity genes (FecB) have additive effect on litter size by increasing ovulation rate. (Davis 2005). So we can use FecB gene for improving litter size. Use of FecB gene in low-input smallholder flocks in India resulted in increased prolificacy in low prolific Deccani ewes with mean litter size of 1.64 (Nimbkar *et al*., 2007).

Major genes controlling litter size:

Numbers of Candidate SNPs in transforming growth factor-β (TGFβ) super family have shown its significant association with ovulation rate and litter size in sheep (Davis 2005). These genes include BMPR-1B, BMP15 and GDF9. Mutations in the Lacaune gene (B4GALNT2) and Woodland gene (FecX2) have been shown to affect ovulation rate and litter size in sheep as well. The mutations have different effects and inheritance patterns. All

mutations increase ovulation rate in heterozygous individuals, but some mutations cause infertility in homozygous individuals where ewes fail to develop ovaries and follicles properly (Gemmell and Slate 2006). The important genes responsible for ovulation rate and litter size in sheep are discussed here under:

Booroola gene

Booroola was the first major fecundity gene detected and the mutation was identified by segregation studies on litter size and ovulation rate in sheep in Australia. It is likely that the mutation was introduced in the Booroola Merino strain from importations of Bengal sheep breed Garole from India in the 1790s (Davis *et al*., 1982; Piper *et al*., 1982). Studies have shown that the Garole sheep is probably the original source of the mutation in the Booroola gene. BMPR-1B, or the Booroola gene, is located on ovine chromosome 6 and codes for bone morphogenetic protein 1B receptors in the ovaries. The detected mutation in the Booroola gene is a single nucleotide non-conservative substitution that has an additive effect on ovulation rate (Davis 2005; Pramod *et al*., 2013).

Lamb survival and birth weight have been reported to be lower among Booroola Merino cross sheep that carry the mutation compared to local breeds without the mutation. It has also been shown that lambs from ewes carrying the mutation need a significantly higher intake of energy and protein per kilogram of average (Visscher *et al*., 2000).

Introgression of the FecB gene into Deccani sheep was studied. Deccani sheep is reared mainly for lamb production in Maharashtra. The mean litter size is low 1.04 (Nimberker *et al*., 2008). The shepherds need a large flock of sheep to get enough number of lambs to sell and sustain their families. So crossed with garole sheep to induced FecB mutation. New breed was named ‘NARI Suwarna’ having mean litter size of 1.65 in homozygous and 1.58 in heterozygous ewes (Table 2). Introgression of the FecB gene into Malpura sheep was also studied (Arora *et al*., 2008). The prolificacy of Garole X Malpura (GMM) crossbred carrying FecB gene was more and also increased litter size compared to native Malpura. Litter size at birth was 1.83 in ewes carrying double copy of the mutation while litter size in non carriers was only 1.01 (Table 3).

Table 2 Garole X Deccani crossbreds Nimbkar *et al* (2008)

Trait / Genotype	FecB++	FecBB+	FecBBB
Live litter size at birth	1.03[a] ± 0.01 (1,632)	1.58[b] ± 0.02 (806)	1.65[b] ± 0.09 (45)
Live litter size at 3 months	0.95[a] ± 0.01 (1,632)	1.35[b] ± 0.02 (806)	1.34[b] ± 0.10 (45)
Total weight of 3-month-old lambs	10.63[a] ± 0.24 (1,326)	13.52[b] ± 0.26 (739)	12.93[b] ± 1.08 (41)

Table 3 Garole X Malpura crossbreds Arora *et al* (2008)

FecB genotype	No. of animals	Litter Size at Birth	Litter size at Weaning	Litter size at 6 month
FecBBB	12	1.83[a] ± 0.21	1.42[a] ± 0.23	1.33[a] ± 0.19
FecBB+	187	1.71[a] ± 0.04	1.46[a] ± 0.05	1.36[a] ± 0.05
FecB++	69	1.01[b] ± 0.01	0.88[b] ± 0.04	0.84[b] ± 0.05

BMP 15 Gene:

The BMP15 gene (also known as FecX or GDF9B) codes for the bone morphogenetic protein 15 is an ovary-derived growth factor that is essential for follicular development in sheep (Hanrahan *et al*., 2004). The action of BMP15 is regulated by the binding protein follistatin and it is important to maintain the granulosa cells responsiveness to FSH (Pramod *et al*., 2013). The mutations in the BMP15 gene increase ovulation rate in heterozygous individuals and decrease in homozygous individuals. (Gemmell and Slate, 2006). Most of the mutations in gene block follicular development in homozygous individuals (Montgomery *et al*., 2001). Two copies of the mutation impair the production of the biologically active mature form of BMP15 which is essential for normal follicular development (Bodin *et al*., 2007). Failure of the BMP15 signaling results in failure of the granulosa cells to divide and support the oocytes which contributes to infertility (Montgomery *et al*., 2001). The BMP15 gene is located on the X-chromosome and to recent date eight different mutations have been discovered in different sheep breeds and populations.

GDF9 Gene:

The GDF9 gene, also called FecG, is located on chromosome 5 and codes for oocyte-derived growth differentiation factor 9 and is essential for normal folliculogenesis (Hanrahan *et al*., 2004). Mutations in the GDF9 gene show similar expression as the BMP15 mutation in the ovaries, however, it increases the ovulation rate in animals even more (Pramod *et al*., 2013).

The mutation in the GDF9 gene increases ovulation rate in heterozygous individuals but in two out of four mutations follicle development is disrupted in homozygous individuals resulting in infertility. (Nicol *et al*., 2009). The ovarian failure is due to a block in follicular growth at an early stage of development. The homozygous phenotype of the ovaries differs from the BMP15 mutations, since the ovarian follicles continue to develop to the antral stages with the majority of the follicles showing abnormal granulosa cells and oocyte morphology. (Pramod *et al*., 2013). Four mutations in the GDF9 gene affecting ovulation rate have been discovered to date. It was first discovered in Belclare and Cambridge sheep (Davis 2005) and rest ones are Thoka mutation (Nicol *et al*., 2009), Embrapa mutation (Silva *et al*., 2011) and mutation in Norwegian white sheep (Vage *et al*., 2013).

Lacaune gene:

The French Lacaune breed is known for its high prolificacy and big litter sizes. Litters with up to four lambs are common and so are high ovulation rates with an average of 5.8 eggs per ovulation which is likely due to several mutations in fecundity genes. Two major genes affecting ovulation rate have been detected in this breed. One is the X-linked BMP15 gene (the mutation in the FecXL allele) and one autosomal gene called the Lacaune gene located at chromosome 11 at the FecL locus (Drouilhet *et al*., 2013). The FecL locus contains two genes, IGF2BP1 (insulin-like growth factor 2 mRNA binding protein 1) and B4GALNT2 (beta-1, 4-N-acetyl-galactosaminyl transferase 2). The Lacaune breed shows an over expression of the B4GALNT2 gene leading to atypical glycosylation of the hormone inhibin in the ovaries, which regulates ovarian functions by inhibiting the secretion of FSH from the anterior pitui-tary gland (Sjaastad *et al* 2003; Drouilhet *et al* 2013). Studies have shown that the B4GALNT2 gene is most likely responsible for the high fecundity in Lacaune sheep. That theory is supported by the fact that B4GALNT2 transferase activity is localized to the granulosa cells which are important in follicular development. The exact position of the mutation on the FecL locus has not yet been identified (Drouilhet *et al*., 2013).

Woodland gene:

The mutation in the Woodland gene, or FecX2, was discovered in 1999 in a screened prolific flock of Coopworth sheep that had a history of interbreeding with Border Leicester and Romney sheep. The gene is located on the X-chromosome, though, the identity of FecX2 and the mechanism by which it affects ovulation rate is unknown to date (Feary *et al*., 2007). Studies have concluded that the Woodland gene is not BMPR-1B or BMP15 (Hanrahan *et al*., 2004). The mutation may affect ovulation rate by changing the expression patterns of

BMP15, BMPR-1B and TGFβR1 in the ovaries. The mutation in the Woodland gene is that it is maternally imprinted which means that it is only ex-pressed in ewes when inherited from their sire (Davis *et al*., 2001). The effect of the mutation is silenced if the ewe inherits it from the dam and will not give an increase in ovulation rate.

Conclusion

Based on the valuable findings of various researchers globally, it could be concluded that the fertility of sheep is very complex phenomenon. Reproductive traits have low heritability, discrete phenotypic expression and are expressed only in sexually mature ewes, leading to the selection of low intensity and long generational intervals. Hence, use of an alternative strategy of identification of SNPs of candidate genes related to fecundity and their use as one of the selection criteria seems to be quite promising for improvement of fertility traits. Genomic approach to the fertility traits will improve the accuracy of selection. The increased accuracy will ultimately pave the way for better economics of livestock farming particularly in small ruminants. Numbers of candidate genes affecting fertility have been found in many sheep breeds around the world. So constant genetic profiling of different breeds should be carried out in search for genes showing significant association with fecundity, fertility and prolificacy and their characterization should be done for better understanding of reproduction traits.

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