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Ezhil Vadhana P
Division of Animal Genetics, ICAR - Indian Veterinary Research Institute, Izatnagar, Bareilly, Uttar Pradesh, India

Ameya Santhosh
Division of Animal Genetics, ICAR - Indian Veterinary Research Institute, Izatnagar, Bareilly, Uttar Pradesh, India

Pooja GS
Division of Animal Genetics, ICAR - Indian Veterinary Research Institute, Izatnagar, Bareilly, Uttar Pradesh, India

Vani A
Division of Animal Genetics, ICAR - Indian Veterinary Research Institute, Izatnagar, Bareilly, Uttar Pradesh, India

Sushil Kumar
Division of Animal Genetics, ICAR - Indian Veterinary Research Institute, Izatnagar, Bareilly, Uttar Pradesh, India

Correspondence
Ezhil Vadhana P
Division of Animal Genetics, ICAR - Indian Veterinary Research Institute, Izatnagar, Bareilly, Uttar Pradesh, India

FecB: A major gene governing fecundity in sheep

Ezhil Vadhana P, Ameya Santhosh, Pooja GS, Vani A and Sushil Kumar

Abstract
Sheep being the major source of income for majority of farming community, holds indispensible position in the livestock and livelihood security of farmers. Major source of income in sheep farming is gained through meat and wool production which can be increased by improving the reproduction efficiency of animals. Selection and Breeding are the two major and basic tools involved in improving the reproduction efficiency. Most of the economic traits have quantitative inheritance, governed by minor genes, however few fecundity genes are exception. Major genes linked with fecundity and fertility have been identified by many researchers. *FecB*, one among them is chiefly involved nowadays in many introgression programmes. Since low heritability of reproduction traits severely hampers the selection, direct selection is very difficult. Marker assisted selection using these major genes linked with reproduction traits can be a best alternative for conventional method of selection.

Keywords: Marker, *FecB*, sheep, fecundity, introgression

Introduction
Fertility being the indispensable parameter controls the production and biological efficiency of sheep [1]. Variation in fertility between and within breeds is controlled by both genetic and environmental factors. Sheep farming is facing a major problem for maximizing production with limited resources in India. With about 43 registered breeds the total sheep population in the country is 65.06 million numbers in 2012, declined by about 9.07% over census 2007 [2]. Sheep (*Ovis aries)* being versatile species, possess more than 900 different breeds differing extensively in their physiological characteristics including ovulation rate and fecundity [3]. Some major genes are responsible for high fecundity in sheep. Use of sheep with *FecB* gene in crossing experiments offers a quantum increase in fecundity in one generation and therefore crossing experiments with the Booroola Merino were undertaken in various countries to evaluate *FecB* and its effects in other breeds [4]. In recent years following identification of *FecB* in the Garole as the likely source of the original mutation, Since then, when Garole was found to be the source of *FecB*, the Garole has been used for crossing experiments with many breeds of sheep [5] in India. Several breeds also shown to carry gene fecundity genes, that have a major effect on fecundity.

In some occasions, major or closely linked minor genes contribute to the differences in the ovulation rate among the animals [6]. Molecular genetics work on sheep has identified the presence of prolificacy genes that have been linked to reproductive efficiency. Molecular genetics and marker assisted selection (MAS) have paramount importance in genetic improvement of reproductive efficiency [7] in sheep. In animal production, marker based investigation have led to identification of several SNPs for traits viz. reproduction [8, 9], production [10, 11], thermotolerance [12, 13] and resistance to diseases like tuberculosis [14, 15, 16, 17, 18, 19], paratuberculosis [20, 21, 22, 23] brucellosis [24] & mastitis [25], along with generalized immune response [26, 27, 28, 29, 30] traits. Multiple genes have been identified of having diversified effects on the prolificacy and efficacy of sheep's reproduction. Age of ewe at service and lambing, and litter size were economically important traits that can enhance the productive value of sheep in terms of improving the twinning rate indirectly improving the meant and wool production. Indirect selection of those marker genes that have been linked to the reproduction traits can be a best alternative for conventional method of direct selection in terms of time and cost incurred.

Fecundity genes
Mutations with major effects on ovulation rate and litter size have been identified in genes of the transforming growth factor beta (TGF-β) super family and a TGF- receptor,

namely bone morphogenetic protein (BMP-15), growth differentiation factor- 9(GDF9) and BMP receptor –IB (ALK6) [31, 32, 33] and some other genes have also been identified. *FecB* or BMPR1B (Bone Morphogenetic Protein Receptor 1B) or ALK6 (activin receptor-like kinase 6) present in chromosome 6, *FecX* or BMP15 (Bone morphogenetic protein 15) present in chromosome X, *FecG* or GDF9 (Growth Differentiation Factor 9) present in chromosome 5 and B4GALNT2 (beta-1,4-N-acetyl-galactosaminyl transferase 2) present in chromosome 11 p [31, 33, 34].

FecB or Booroola gene

Origin of mutation was traced back by Turner [35] and expanded by Piper and Bindon [4]. Turner and Young [36] visualized high prolificacy of separate line of Booroola merino (Australia) compared to other merino flock and those animals were selected for breeding experiments for improving the prolificacy. Simultaneously with Australian Flock Registers they traced back and found that the origin of *FecB* should be from Garole Breed of India which arrived in Australia from Kolkata in 1792 so called Bengal sheep at that time. A major gene, located in the BMPR1B gene, which is linked to the increase in fecundity of Booroola Merino was named *FecB* by the Committee on Genetic Nomenclature of Sheep and Goats. Possess a mutation (A746G) in its coding region leading to amino acid substitution (Q249R) in its protein sequence. In Booroola ewes, *FecB* gene, which is mapped to sheep chromosome 6q23–31, has additive effect on ovulation rate and partially dominant effect on litter size, can be inherited as a single autosomal locus and is syntenic to human chromosome 4q21–25. Heterozygous carrier parents produced approximately 1.5 extra eggs, giving birth to approximately 1.0 extra lamb per lambing. Homozygous carriers produced about 3.0 extra eggs producing about 1.5 extra lambs per lambing [37]. In addition to its effect on granulosa cells, *FecB* also affects the development of oocyte and its function.

Mechanism of Action

The members of the transforming growth factor beta (TGF-β) superfamily of peptides including bone morphogenetic proteins (BMPs) and activins were bound for the coordination of development and homeostasis of many tissues in various animal species right from insects (fruit fly) to mammals [38]. The TGF-β signal transduction network possess a receptor serine/threonine kinase at the cell surface, after binding of a ligand to its type 2 receptor in concert with a type 1 receptor, leads to a formation of heterodimeric receptor complex and phosphorylation of the type 1 receptor. Once activated, the type 1 receptor phosphorylates a receptor-regulated Smad which then heterodimerizes with a common Smad (Smad-4) and moves to the nucleus where the Smad complex associates with nuclear transcription factors and activates transcription of target genes [39].

Granulosa cells and oocytes expresses BMPR1B through all the stages of development and to a lesser extent by the theca layer of antral follicles also [40]. It has been reported as a potent receptor for various BMP (Bone Morphogenetic Protein) factors [41]. Basal and FSH-stimulated progesterone production can be inhibited by Ovine granulose cells from small antral follicles, BMP-2, 4 and 6 receptors. BMP-2, 4 and 6 also enhances gonadotropin-induced estradiol production and decreases LH-induced androstenedione production [42]. All the above discussed factors were promising stimulators of theca cells proliferation. *FecB* mutation (Q249R), being hypothesized as a partial "loss of function" mutation, is associated with the loss of responsiveness of BMP-4 receptor to the inhibitory action of progesterone production [43], and hence by decreasing BMP activity indirectly increases the ovulation rate. Through loss of function activity, allows numerous maturation of LH-responsive follicles with lower number of granulose cells, producing same amounts of estradiol and inhibin as non-carriers [44]. Marked differentiative response to BMP, gonadotropin, and IGF-I stimulation has been shown by the granulose and theca cells of carrier ewes on tissue culture studies and thereby explains the mechanism of deregulating the normal follicle selection process by its profound effect in inducing precocious maturation of ovarian follicles. The mechanism by which the carrier ewes differs from the non-carriers are not because of the total number of antral follicles but due to the markedly extended recruitment period along with low prevalence of atresia which leads to maturation and ovulation of large number of small ovulatory follicles. Some research studies strongly denote that the effect of *FecB* on ovulation rate is by altering the response of ovary rather than the level of gonadotropins applied to the ovary.

FecB on Growth traits

Some of the researches observed that the lambs carrying the Booroola mutation exhibit relatively lower birth weight and growth rates compared with non- carrier lambs [45,46]. Lamb survival also has been reported to be lower among Booroola merino cross sheep carrying mutation. Lambs of carrier ewes require comparatively higher energy and protein per kilogram in an average [47]. Since lambs carrying the Booroola mutation are often from large litters, it is not clear whether their low birth weight, reduced postnatal growth and smaller mature body size is the result of the lambs being born in large litters or the result of a direct negative effect of the *FecB* locus on growth ability. Quantitative trait locus for low weaning weight has been suggested to segregate with the booroola mutation [48]. And this may explain some of the inferiority in the growth rate of booroola lambs. Report says that the gene has negative impact on fetal development [49] resulting in comparatively low birth weight.

Metabolic effects of *FecB*

Global metabolomics studies showed that in carrier animals, the mutation has marked effect on FF (Follicular Fluid) than in OVS (Ovine Vein Serum). Changes in the FF might affect the growth of the developing oocyte. Biochemical studies showed that the higher oxidative pressure of rapidly dividing cells in the homozygous animals, resulted in a greater antioxidant capacity of the FF. Additionally, some key metabolites in ovine FF samples were found to significantly correlate with ovulation rate. Altogether, *FecB* mutation not only affects ovulation rate but also the metabolic profile of FF [50].

FecB on male reproductive system

In addition to its effect on female reproduction, *FecB* also have its effect on male reproduction by significantly affecting percent linearity and rapid motility of sperms, which did not change significantly with age. Although, homozygous carrier animals have increased sperm concentration than heterozygous which in turn was higher than non-carriers, this effect was non-significant. The age and *FecB* mutation have

significant effects on velocity and percentage of motile sperms without influencing the sperm morphometry [51]. A report says that *FecB* is also responsible for the rate of increase of FSH concentration in adult rams after castration [52] which is the reason for higher sperm concentration of homozygous and heterozygous Garole x Malpura rams.

Breeds possessing *FecB*

A number of prolific breeds all over the world were screened for *FecB*, besides Garole and Booroola, the mutated gene was present in Javanese (Indonesia), Small Tailed Han (China) [53,54,55], and Hu (China) sheep [54,55,56]. *FecB* mutation in Garole [57], Kendrapada [58] and Nilagiri sheep [59] were reported in India. Studies shows that the mutation in fixed only in the Garole and Hu sheep population but segregating in other breeds wherein which it is present and because of its segregating nature, it has spread to about 48 breeds and synthetics in about 19 different countries [60].

Conclusion

By improving the prolificacy, economic contribution of the *FecB* gene, can be noticed as early as in first generation itself after introgression, where the farmers income is mainly based on the lamb production. Introgression of the Booroola gene has an obvious potential for quick and large improvement of sheep breeding through cross breeding programmes which can improve the economic status of farmers who depend entirely on Sheep farming. Being affected by Environmental conditions, Ewe parity, Breed effect, Other genes, Flock management, Nutrition and Uterine capacity Introgression into new breed has its own utility and disadvantages. Constant genetic profiling of various prolific breeds in search of genes associated with fecundity, fertility and prolificacy and their molecular characterization can be done for better understanding. Detailed research is needed to search and evaluate the mutations in other fragments of the major genes and related genes in various other breeds and populations such that marker assisted selection can be rendered as a great tool for increasing the prolificacy of sheep and thereby helping the farmers for increasing their livelihood security.

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