



Bone Morphogenetic Protein (BMP15) Gene and its Relationship with Prolificacy in Sheep (Review Paper)

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ABSTRACT

This review aims to study the Bone Morphogenetic Protein (BMP-15) gene and its association with ovulation rate and litter size in sheep. Fecundity traits such as ovulation rate and litter size are genetically regulated by many genes with small effects, and sometimes also by a single gene with major effects. BMP15 is essential for activation of the primordial follicle and subsequently in all stages of normal follicular development, maturation and ovulation. Mutations in the BMP-15 gene have been observed to be associated with increased ovulation rate and litter size in many sheep breeds worldwide.

Keywords: *BMP-15 gene; Relationship; Prolificacy; Sheep.*

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Introduction

Reproductive traits are often suggested as prime targets for marker assisted selection (MAS) because of their low heritability, the fact that the trait can be measured only in one sex and rather late in life. Ovulation rate (i.e. the number of mature oocytes released during one reproductive cycle) in mammals is determined by a complex exchange of hormone signals between the pituitary gland and the ovary, and by a localized exchange of hormones within ovarian follicles between the oocyte and its adjacent somatic cells (Galloway *et al.*, 2000; Eppig, 2001). Genetic improvement of reproductive performance could be achieved either by direct selection for a composite trait or by selection for one of the component traits. It is important to determine whether direct selection for total weight of lamb weaned per ewe joined is more efficient than selection for number of lambs born, number of lambs born weaned or weaning weight (Olivier *et al.*, 2001). Until recently, emphasis has mostly been placed on the individual component traits of reproduction such as fertility, litter size, lamb survival rate and the number of lambs born and weaned per ewe joined (Duguma *et al.*, 2002).

Reproduction is a complex process and fecundity traits such as ovulation rate and litter size can be genetically regulated by many genes with small effects, and sometimes also by single genes with major effects, called fecundity (Fec) genes (Drouilhet *et al.*, 2009). By DNA testing rams and ewes for major genes and learning about inheritance patterns, sheep producers have been given the ability to increase ovulation rate and litter sizes and thereby productivity (Davis, 2005). It is important to note that breeding for an optimal and constant litter size should be more desirable than trying to increase the number of lambs born per ewe (SanCristobal-Gaudy *et al.*, 2001). The optimal litter size may differ between production systems, climate, breeds and the availability of nutritious forage. The BMP receptor is expressed by oocytes and granulosa cells from the primary stage to the late antral stage of follicle development and

binds to BMP-15. Mutation in the BMPR-1B gene is a single nucleotide non-conservative substitution that has an additive effect on ovulation rate (Davis, 2006; Pramod *et al.*, 2013). A single copy of the gene in heterozygous ewes produced about 1.5 extra eggs and gave birth to about 1.0 extra lamb per ewe lambing. Homozygous ewes carrying two copies of the gene produced about 3.0 extra eggs resulting in about 1.5 extra lambs per ewe lambing (Davis, 2004).

The aim of this review is to study the BMP-15 gene that is associated with ovulation rate and litter size in sheep, and can be used as a genetic marker in multi-gene pyramiding for improving litter size in sheep husbandry (Wang *et al.*, 2015). This gene in some way involved in ovulation rate and litter size in sheep but have different effects and inheritance patterns. Many studies conducted in this field and new genes and mutations affecting fertility are being discovered constantly.

BMP-15 gene

Bone morphogenetic protein 15 (BMP15), also known as growth differentiation factor 9B (GDF9B), was identified by two independent groups, in 1998. The first group used polymerase chain reaction (PCR), utilizing degenerate oligonucleotides, based upon consensus sequences from known BMP's, to identify both the mouse Bmp15 and human BMP15 genes (Dube *et al.*, 1998). The second group searched the Gen Bank Expressed Sequence Tag (EST) database with the mouse GDF9 sequence. From this search, they identified a putative member of the TGFB superfamily from a mouse 2-cell embryo library, which they named GDF9B (Laitinen *et al.*, 1998). BMP15 has also been reported as ovarian dysgenesis 2 (ODG2) (Di Pasquale *et al.*, 2004) and as premature ovarian failure-4 (POF4) (Dixit *et al.*, 2006). Bone morphogenetic protein-15 (BMP-15) genes belongs to the TGF β (Transforming growth factor- β) family, which acts as a key regulator of granulosa cell (GC) processes in ovarian follicular development (Galloway *et al.*, 2000;

Hanrahan *et al.*, 2004). The sheep BMP-15 gene is located on the X chromosome (Galloway *et al.*, 2000). The c.718C>T mutation (named FecX^G; Galway mutation) in BMP-15 gene was first identified in Cambridge and Belclare sheep, which increased ovulation rate and infertility (Bodin *et al.*, 2007).

Human BMP15 (hBMP15) is encoded by a gene on the X chromosome at location Xp11.2 (Dube *et al.*, 1998). The gene consists of two exons. Exon 1 codes for part of the pro-region while exon 2 codes for the remainder of the pro-region and the entire mature region. The gene product of hBMP15 is a 39-amino acid (aa) preproprotein consisting of a 17-aa signal peptide, a 251aa pro-region and a 124aa mature region. Like other members of the TGFB superfamily, BMP15 is synthesized as a prepropeptide that requires cleavage, by a furin-like proprotein convertase, at an arginine rich cleavage site (RRXR), to produce a mature protein. However, the specific proprotein convertase that functions in this capacity is presently unknown.

In sheep, BMP15 is essential for activation of primordial follicle and subsequently in all stages of normal follicular development, maturation and ovulation (Bodensteiner *et al.*, 1999; Eppig, 2001; Juengel *et al.*, 2002). Mutations in the BMP-15 gene have been found associated with increased ovulation rate and fertility (Hanrahan *et al.*, 2004). Polymorphism in the BMP15 gene was found to be associated with increased ovulation rate in Inverdale (FecXI) and Hanna (FecXH) sheep (Galloway *et al.*, 2000).

Biological functions of BMP15 regulating follicular development

Growth differentiation factor 9 (GDF9) and BMP15 alone and in combination suppressed FSH-stimulated progesterone production and stimulated cell proliferation. Both GDF9 and BMP15 have species dependent effects. In ovine granulosa cells, ovine BMP15 given together with mouse GDF9 or ovine GDF9 was more potent in stimulating ovine

granulosa cells mitosis compared with each growth factor independently, while in bovine granulosa cells there is little or no co-operative action between ovine BMP15 and GDF9 in terms of mitotic activity (McNatty *et al.*, 2005a). Higher ovulation rate in BB sheep (homozygous for a mutation in the bone morphogenetic protein receptor type 1B (BMPR1B) is due, at least in part, to lower oocyte-derived BMP15 mRNA levels together with the earlier onset of LH-responsiveness in GC (Crawford *et al.*, 2011).

The Action of BMP-15 and its expression in the ovary

The action of BMP15 is regulated by the binding protein follistatin, which can bind in BMP15 and inhibit its effect on the oocyte. BMP15 inhibits FSH receptor expression in the ovaries, thus follistatin is important to maintain the granulosa cells responsiveness to FSH (Pramod *et al.*, 2013). The BMP15 mutations differ slightly in type and effect. The Rasa Aragonesa mutation is an amino acid deletion while the Galway and Hanna mutations are premature stop codons. The other mutations are likely to be amino acid substitutions that alter the shape of the proteins thereby changing their function (Demars *et al.*, 2013). There is strong evidence to point out that bone morphogenetic protein -15 is responsible for the developing secondary follicles from primordial follicles from the ovary. The mechanism of action of bone morphogenic protein is thought to be either by direct stimulation of the ovary or influence of the specific growth differential factors (Saito, 2008).

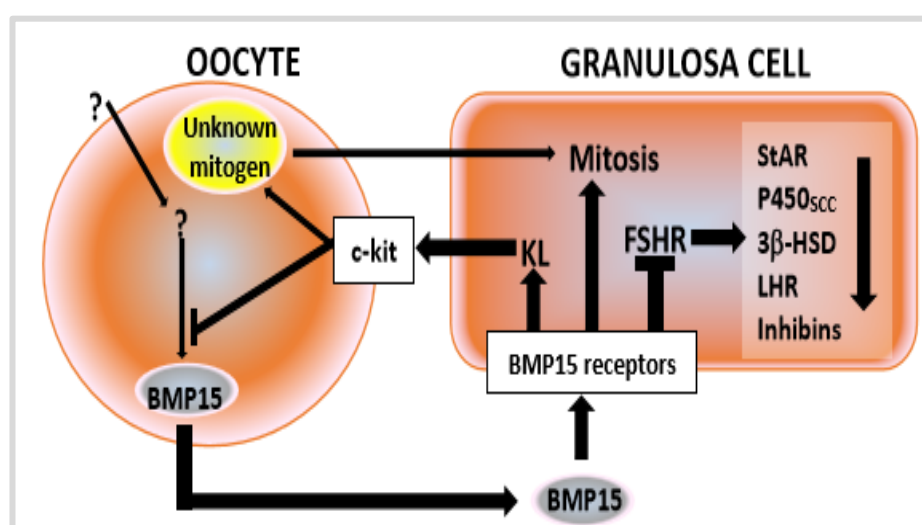
Action of this bone morphogenetic protein – 15 is similar in many ways like the growth differentiation factor gene – 9. Many studies have indicated that bone morphogenetic protein has a role to play in maturation of the developing oocyte and development of secondary ovarian follicles from primordial ovarian follicles. Defective bone morphogenetic protein results in defective ovary (Di Pasquale, 2004). During folliculogenesis and oocyte maturation in mammals, BMP signaling affects female fertility by regulating various traits, including

ovarian hormone secretion, gonadotropin receptor gene expression and oocyte quality. BMP pathway members have also been associated with ovulation rate and normal estrous cycling, processes that are tightly regulated by hormone signaling in the ovary. In humans, rats, sheep, and cows, progesterone secretion by granulosa cells is suppressed by BMP ligands (Zhang *et al.*, 2015). In contrast, however, BMP15 has no effect on granulosa cell progesterone levels in sheep (McNatty *et al.*, 2005). In sheep, BMP15 is essential for activation of primordial follicle and subsequently in all stages of normal follicular development, maturation and ovulation (Juengel *et al.*, 2002; Mandon-Pepin *et al.*, 2003). Mutations in the BMP-15 gene have been found associated with increased ovulation rate and fertility (Hanrahan *et al.*, 2004). Polymorphism in the BMP15 gene was found to be associated with increased ovulation rate in Inver dale (FecXI) and Hanna (FecXH) sheep (Galloway *et al.*, 2000).

Bone morphogenetic protein (BMP15) is expressed specifically in the oocyte from the beginning of formation of one-layer primary follicle and it continues till ovulation (Sun *et al.*, 2010). In sheep and cattle (Bodensteiner *et al.*, 1999), oocyte expression of GDF9 mRNA begins at the primordial follicle stage but BMP15 is detected only in oocytes from the primary follicle stage onward in sheep. However, BMP15 was found in oocytes and Granulosa Cells of all follicles in mouse and porcine. GDF9, c. BMP15 and their receptors might correlate with primordial follicular recruitment in pig.

The figure 1. Adapted from (Otsuka and Shimasaki, 2002) in the rat, BMP15 binds to its receptor on granulosa cells and inhibits FSH-R expression, the consequence of this is that, mRNA for StAR, P450SCC, 3 β HSD, LH receptor and the inhibin- α and activin β A & β B subunits are all subsequently inhibited in response to FSH. BMP15 also stimulates mitosis both directly and possibly via a kit ligand (KL)/c-kit mediated pathway. In turn KL acting via c-kit inhibits the expression of BMP15 in

a negative feedback loop. It is not known what signal (s) stimulates BMP15 expression.



Source: (Otsuka and Shimasaki 2002)

Figure 1. The role of BMP15 in a cross-talk between oocytes and granulosa cells in rat

Ovulation Rate and Litter Size in Sheep

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 (Souza *et al.*, 2001). Beside genetic background, the variation in ovulation rate between breeds can be influenced by age, season and nutrition. Litter size differs between and within sheep breeds (Davis, 2005). It is a trait that depends on ovulation rate and is affected by the number of fertilized oocytes. The higher the ovulation rate, the more oocytes will be available for fertilization during

the estrous and increase the possibility of bigger litters (Drouilhet *et al.*, 2013). It has not been proven that there is a genetic difference between sheep breeds in the ability to support fertilized eggs in the uterus, although, an excess number of fetuses in mono-ovulatory species like sheep can result in major embryo loss (Souza *et al.*, 2001). Studies have shown that higher ovulation rates result in reduced embryo survival and bigger litter sizes lowers the birth weights of lambs (Fogarty, 2009). Genetic mechanism caused by mutations in BMPR-1B and BMP-15 genes, which has a relationship with the average number of ovulations in sheep, is still not widely known. The tendency for sheep producing twins (twining) or three (triplets) lambs are the same, although there are differences in the level of gene regulation.

Table 1. Mean ovulation rate and percentage increase above (WT) in various sheep breeds/lines with heterozygous mutations in GDF9, BMP-15 or ALK6 or combinations thereof.

Wild-type or mutation	Predicted effect on BMP15, GDF9 or receptor type	Hanna ^a	Inverdale ^a	F700 Belclare ^b	Cambridge ^b	Booroola ^c
WT	None	1.8	1.8	1.9	2.3	1.7
FecX ^H (BMP15)	Reduced BMP15 concentrations	3.0 (+67%)	–	–	–	–
FecX ^I (BMP15)	Reduced BMP15 concentrations	–	2.9 (+61%)	–	–	–
FecX ^G (BMP15)	Reduced BMP15 concentrations	–	–	2.7 (+42%)	3.1 (+35%)	–
FecX ^B (BMP15)	Reduced BMP15 concentrations or interaction with type 2 receptor	–	–	3.7 (+95%)	–	–
FecG ^H (GDF9)	Altered interaction or reduced BMP15 concentrations with type 1 receptor	–	–	–	4.3 (+87%)	–
FecB ^B (ALK6)	Altered BMP15 signalling	–	–	–	–	3.0 (+76%)
FecX ^G and FecG ^H	Reduced BMP15 concentrations and altered interaction with type 1 receptor	–	–	–	5.8 (+152%)	–
FecX ^B and FecG ^H	Altered interactions with types 1 and 2 receptor	–	–	6.1 (+221%)	–	–
FecB ^B and FecX ^I	Reduced BMP15 concentrations and altered BMP15 signalling	–	–	–	–	4.4 (+159%)

WT, wild-type animals.

^a Davis *et al.* (2001). ^b Hanrahan *et al.* (2004). Davis *et al.* (1999).

BMP-15 Mutations and litter size in Sheep

Five naturally mutations in exon 2 of the sheep BMP-15 gene have been identified, FecX^G (Gallway), FecX^B (Belclare), FecX^I (Inverdale), FecX^H (Hanna), FecX^L (Lacaune), and cause infertility in homozygous ewes due

to defects in early stages of folliculogenesis (Galloway *et al.*, 2000, Hanrahan *et al.*, 2004, McNatty *et al.*, 2005, Bodin *et al.*, 2007). It has been well documented that heterozygote carriers for BMP15 mutations display an increased ovulation rate and litter size compared to the wild-type ewes (Galloway *et al.*, 2000; Hanrahan *et al.*, 2004; Bodin *et al.*, 2007; Monteagudo *et al.*, 2009). The majority of these mutations were located in the propeptide region of BMP15 or GDF9 (Di Pasquale *et al.*, 2004; Iagaki and Shimasaki, 2010; Abdoli *et al.*, 2016). The propeptide region of the protein is one of the most important attributes affecting the post-translational processing of the transforming growth factor beta (TGF β) superfamily (Liao *et al.*, 2003; Shimasaki *et al.*, 2004; Di Pasquale *et al.*, 2004). The same FecB mutation (Q249R) occurred in the BMPR1B gene in Small Tailed Han ewes as found in Booroola Merino ewes. An equivalent FecX^B mutation (Q239Ter) of the BMP15 gene was found in Small Tailed Han ewes as in Belclare and Cambridge ewes. The Small Tailed Han ewes carrying mutations in both BMPR1B and BMP15 genes had greater litter size than those with either mutation alone (Chu *et al.*, 2007).

Table 2, shows the information of the mutations founder breed, name, and allele symbol and chromosome location in sheep. The effect on ovulation rate and litter size is a comparison between heterozygous (A+) and homozygous (AA) to non-carriers of the mutations (++) rounded to one decimal place.

The differences in expression levels of BMP15 and BMPR1B may play a role in the increase in ovulation rate observed in Woodlands ewes with FecX2^w mutation (Feary *et al.*, 2007). The inhibitory effect of BMPs and GDF9 on FSH secretion was significantly greater in pituitary cells harvested from Booroola homozygous carrier of BMPR1B mutation when compared with non-carrier animals (Young *et al.*, 2008). The Inverdale (FecX^I) and Hanna (FecX^H) mutations were the first two mutations in the BMP15 gene to be discovered. Both mutations were found in New Zealand in the 1990s, in highly prolific populations of Romney sheep where one ewe had produced 33 lambs in 11 lambing's.

Although both mutations give a similar phenotype and are the result of a single nucleotide substitution, Inverdale affects the mature coding sequence while Hanna results in a premature stop codon. Ewes that are heterozygous with the Inverdale or Hanna mutation show an increase in litter size, while homozygous ewes have small, undeveloped ovaries which results in infertility (Davis, 2005). (Montgomery *et al.*, 2001) suggested that the Inverdale and the Hanna sheep mutation were located on the same locus and showed this by crossing sheep homozygous with one of the mutations respectively, thus creating the phenotype $FecX^I/FecX^H$. The researchers confirmed their hypothesis as the resulting ewes were infertile with undeveloped ovaries, phenotypically indistinguishable from ewes heterozygous with the Inverdale mutation.

Table 2. Mutations in the fecundity genes BMPR-1B, BMP15, and GDF9, B4GALNT2 (beta-1, 4-N-acetyl-galactosaminyl transferase 2, Lacaune gene) and FecX2 (fecundity gene X2, Woodland gene) and their effect on ovulation rate and litter size in sheep.

Gene	Founder Breed	Name, allele symbol	Chromosome	Effect ovulation rate	Effect litter size	Reference
BMPR-1B	Booroola Merino, (Garole)	Booroola, $FecB^B$	6	B+: +1.3 BB: +3.6	B+: +0.7 BB: +0.8	¹
BMP15	Romney	Inverdale, $FecX^I$	X	I+: +1.0 II: infertile	I+: +0.6 II: infertile	²
BMP15	Romney	Hanna, $FecX^H$	X	H+: +1.0 HH: infertile	H+: +0.6 HH: infertile	²
BMP15	Belclare	Belclare, $FecX^B$	X	B+: +1.0 BB: infertile	- BB: infertile	²
BMP15	Belclare and Cambridge	Galway, $FecX^G$	X	G+: +0.7 GG: infertile	- GG: infertile	²
BMP15	Lacaune	Lacaune, $FecX^L$	X	L+: +2.0 LL: infertile	- LL: infertile	⁴
BMP15	Rasa Aragonesa	Rasa Aragonesa, $FecX^R$	X	- RR: infertile	R+: +1.3 RR: infertile	⁵
BMP15	Grivette	Grivette, $FecX^{Gr}$	X	- -	Gr+: +1.9 GrGr: +2.5	³
BMP15	Olkuska	Olkuska, $FecX^O$	X	O+: +2.0 OO: +3.3	- -	³
GDF9	Belclare and Cambridge	High Fertility, $FecG^H$	5	H+: +1.4 HH: infertile	- HH: infertile	²
GDF9	Icelandic	Thoka, $FecG^T$	5	I+: +1.2 II: infertile	I+: +0.7 II: infertile	²
GDF9	Santa Inês	Embrapa, $FecG^E$	5	- EE: +1.0	- EE: +0.7	³
B4GALNT2	Lacaune	Lacaune, $FecL^L$	11	L+: +1.5 LL: +3.0	L+: +1.0 LL: +2.0	^{7,8}
FecX2	Coopworth	Woodland, $FecX2^W$	X	W+: +0.4 WW: $\geq +0.4$	W+: +0.3 WW: $\geq +0.3$	²

¹ Fogarty, 2009, ² Davis, 2005, ³ Demars *et al.*, 2013, ⁴ Bodin *et al.*, 2007, ⁵ Monteagudo *et al.*, 2009, ⁶ Våge *et al.*, 2013, ⁷ Drouilhet *et al.*, 2009 and ⁸ Drouilhet *et al.*, 2013

CONCLUSION,

In conclusion, the BMP15 is essential for activation of the primordial follicle and subsequently in all stages of normal follicular development, maturation, and ovulation. Mutations in the BMP-15 gene have been observed to be associated with increased ovulation rate and litter size in many sheep breeds worldwide.

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Bone Morphogenetic Protein (BMP15) Gene and its Relationship with Prolificacy in Sheep (Review Paper)

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المستخلص

تهدف هذه الورقة الاستعراضية لدراسة جين الخصوبة (BMP15) وعلاقته بمعدل التبويض وعدد الأجنة في البطن الواحدة في الاغنام. صفات الخصوبة - من الناحية الوراثية - مثل معدل التبويض وعدد الأجنة في البطن الواحدة يتم تنظيمه بواسطة عدد من الجينات ذات تأثيرات صغيرة وأحياناً بواسطة جين واحد ولكن تأثيراته كبيرة. جين الخصوبة BMP15 ضروري من أجل تنشيط البويضات الأولية وبالتالي تنشيط كل مراحل تطور ونمو البويضات السليمة، انضاجها واخصابها. الطفرور الذي يحدثه جين الخصوبة (BMP15) في الاغنام حتي الآن قد لوحظ ارتباطه بزيادة معدل التبويض وعدد الأجنة في البطن الواحدة في عدد من الاغنام حول العالم.

كلمات مفتاحية: جين BMP-15، خصوبة؛ ضأن.

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