



# Pleomorphic adenoma gene1 in reproduction and implication for embryonic survival in cattle: a review

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## Abstract

The pleomorphic adenoma gene1 (*PLAG1*) encodes a DNA-binding, C<sub>2</sub>H<sub>2</sub> zinc-finger protein which acts as a transcription factor that regulates the expression of diverse genes across different organs and tissues; hence, the name pleomorphic. Rearrangements of the *PLAG1* gene, and/or overexpression, are associated with benign tumors and cancers in a variety of tissues. This is best described for pleomorphic adenoma of the salivary glands in humans. The most notable expression of *PLAG1* occurs during embryonic and fetal development, with lesser expression after birth. Evidence has accumulated of a role for *PLAG1* protein in normal early embryonic development and placentation in mammals. *PLAG1* protein influences the expression of the *ike growth factor 2 (IGF2)* gene and production of IGF2 protein. IGF2 is an important mitogen in ovarian follicles/oocytes, embryos, and fetuses. The *PLAG1-IGF2* axis, therefore, provides one pathway whereby *PLAG1* protein can influence embryonic survival and pregnancy. *PLAG1* also influences over 1,000 other genes in embryos including those associated with ribosomal assembly and proteins. Brahman (*Bos indicus*) heifers homozygous for the *PLAG1* variant, rs109815800 (G > T), show greater fertility than contemporary heifers with either one, or no copy, of the variant. Greater fertility in heifers homozygous for rs109815800 could be the result of early puberty and/or greater embryonic survival. The present review first looks at the broader roles of the *PLAG1* gene and *PLAG1* protein and then focuses on the emerging role of *PLAG1/PLAG1* in embryonic development and pregnancy. A deeper understanding of factors which influence embryonic development is required for the next transformational increase in embryonic survival and successful pregnancy for both in vivo and in vitro derived embryos in cattle.

## Lay Summary

The pleomorphic adenoma gene1 (*PLAG1*) produces *PLAG1* protein which, by binding to specific regions on DNA, influences the activity of other genes that regulate many body functions. One gene is insulin-like growth factor 2 (*IGF2*) which controls cell metabolism and growth. The *PLAG1* gene is particularly active during embryonic and fetal growth, and through *IGF2* determines stature later in life. IGF2 protein is also very important in early embryonic development. This review explores the hypothesis that *PLAG1* is an important determinant of embryonic survival and the establishment of pregnancy in mammals.

**Key words:** cattle, embryo, pleomorphic adenoma gene, *PLAG1*

**Abbreviations:** CBV, Collins Belah Valley; CHCHD7, coiled-coil-helix-coiled-coil-helix domain containing 7; EBV, estimated breeding value; IGF2, insulin-like growth factor 2; LIF, leukemia inhibitory factor; *PLAG1*, pleomorphic adenoma gene 1

## Introduction

The major cause of reproductive loss in cattle is the failure of embryos to progress to implantation and pregnancy. Fertilization rates in both beef and dairy cattle are in the order of 85% to 100%; however, only 40% to 60% of embryos establish a pregnancy (Diskin et al., 2016; Lockhart et al., 2023). In recent reviews, we have argued that the next transformational change in reproductive efficiency will require a deeper understanding of the biology of early embryo development in cattle (D'Occhio et al., 2019b, 2020a, b; Campanile et al.,

2021). This applies to both natural mating and assisted reproduction. A critically important feature of early embryo development is the dialogue between embryo and uterus in the period before embryo attachment and during implantation (Hantak et al., 2014; Rizos et al., 2017; Sponchiado et al., 2017, 2019, 2020; Aguilera et al., 2022; Binelli et al., 2022; Cajas et al., 2022; Tesfaye et al., 2022). Factors involved in embryo-uterine communication include the transforming  $\beta$  superfamily (D'Occhio et al., 2020a), cell-cell adhesion molecules (D'Occhio et al., 2019b), kisspeptin (D'Occhio et al.,

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2020b) and immune factors (Campanile et al., 2021), among others. Our reviews, and those of others, have noted the complexity of events associated with early embryo development, attachment of the conceptus to the uterine epithelium, and implantation. The reviews have identified major gaps in our understanding of early embryo development in cattle. The gaps in knowledge largely explain the relatively modest progress over the past 40 yr in reducing high embryo loss in cattle. High embryo loss applies to both in vivo and in vitro derived embryos. Embryo loss is comparable after natural mating, artificial insemination, or embryo transfer (Hansen, 2020). The transfer of a bovine embryo to a recipient at day 7 of development avoids the relatively large loss of embryos that occurs in the first 7 d after fertilization. However, there is still considerable loss between the transfer on day 7, and day 21, when embryo attachment has commenced (Hansen, 2020). Therefore, the transfer of a bovine embryo on day 7 of early development does not overcome all the embryo losses in cattle that occur before implantation.

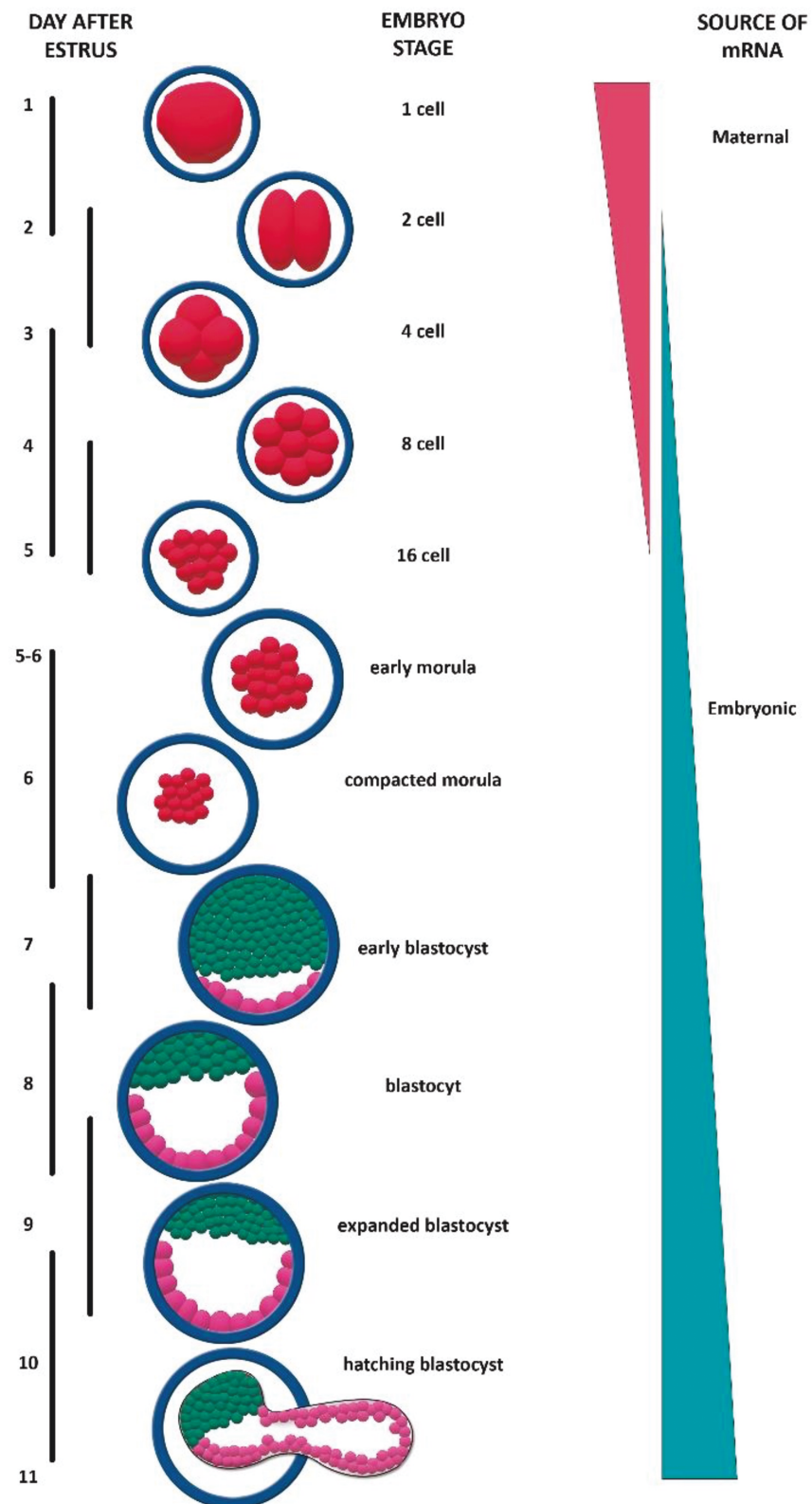
The present review seeks to build on our earlier articles and looks at the potential role of the pleomorphic adenoma gene 1 (*PLAG1*) in early embryonic development. The *PLAG1* gene encodes a DNA-binding, C<sub>2</sub>H<sub>2</sub> zinc-finger protein which acts as a transcription factor that regulates the expression of diverse genes across different organs and tissues (Voz et al., 2004; Abdollahi, 2007; Wagner and Zhang, 2011; Adnani et al., 2018). The most notable expression of *PLAG1* occurs during embryonic and fetal development with lesser expression after birth (Hensen et al., 2004; Tang et al., 2013; Habib et al., 2018; Madissoon et al., 2019; Li et al., 2020a). There is a paucity of information on the transcriptional regulation of the *PLAG1* gene. The neurogenic factor Hmga2 induces expression of *PLAG1* in neuronal progenitor cells (Sakai et al., 2019) while microRNA-141 shows translational regulation of *PLAG1* mRNA (Tang et al., 2013). In early embryos, *PLAG1* protein was reported to act at conserved Alu/B1 elements in the promoter region of over 1,000 genes associated with ribosomal assembly and protein synthesis (Madissoon et al., 2019). Rearrangements of the *PLAG1* gene, and/or overexpression, are associated with benign tumors and neoplasia in different tissues (Matsuyama et al., 2011). This is best described for pleomorphic adenomas of the salivary glands in humans, which gave the gene its name (Voz et al., 1998, 2000; Åström et al., 1999; Debiec-Rychter et al., 2001; Hensen et al., 2002; Declercq et al., 2005; Asp et al., 2006; Van Dyck et al., 2007; Skálová et al., 2021). There is evidence of a role for *PLAG1* protein in normal early embryonic development and placentation. In mice, oocytes with low amounts of maternal *PLAG1* transcripts showed a delay in zygotic genome activation, and 2-cell-stage embryonic development (Madissoon et al., 2019). The *PLAG1* gene is maternally imprinted and an ongoing role for *PLAG1* protein during embryonic development may depend on the expression of paternal *PLAG1* (Moore & Haig, 1991; O'Doherty et al., 2012; Barlow & Bartolomei, 2014; Plasschaert & Bartolomei, 2014; Adhami et al., 2015; Jiang et al., 2015; Lafontaine et al., 2020). In cattle, minor activation of the embryonic genome occurs at the 2-cell embryo stage, with major activation at the 4- to 8-cell stage (Telford et al., 1990; Memili et al., 1998; Memili & First, 1999, 2000; Dean et al., 2001; Kaňka et al., 2003; Meirelles et al., 2004; Ruddock et al., 2004; Gad et al., 2012; Ozawa et al., 2012; Graf et al., 2014a, b; O'Doherty et al., 2015; Jukam et al., 2017; Jiang et al., 2018; Lavagi et al., 2018; Duan et al., 2019;

Halstead et al., 2020; Ivanova et al., 2020; Figure 1). *PLAG1* is polymorphic in cattle and any potential action of *PLAG1* protein on ongoing embryonic development may depend on the nature of the paternal *PLAG1* allele. *PLAG1* can influence the production of IGF2, H19, leukemia inhibitory factor (LIF),  $\beta$ -catenin, and cytokines. These factors are all variously associated with embryonic development, uterine attachment, and implantation (Niemann & Wrenzycki, 1999; Han et al., 2003; Gabory et al., 2009; Agrogiannis et al., 2014; Jiang et al., 2015; Smith et al., 2015; Sferruzzi-Perri et al., 2017; Campanile et al., 2021; Llobat, 2021; Willhelm et al., 2021; Zhou et al., 2021; Sandovici et al., 2022). The role of LIF and other cytokines, and the LIF receptor, in embryonic development and implantation is comprehensively discussed in earlier reviews which are complemented by the present review (Guzeloglu-Kayisli et al., 2009; Robertson et al., 2018; Campanile et al., 2021; Namiki et al., 2023). The role of catenins during early vertebrate development through cell adhesion in association with cadherins (Stepniak et al., 2009; D'Occhio et al., 2019b) and intracellular signaling in the Wnt/ $\beta$ -catenin pathway (Valenta et al., 2012; Liu et al., 2022) also have been well documented. In cattle, polymorphisms of the *PLAG1* gene are linked with fetal and postnatal growth and adult phenotypes including fertility (*PLAG1* and Phenotype in Cattle below).

The approach adopted in the present review is to first provide a general background on the *PLAG1* gene and *PLAG1* protein. We then consider relationships between *PLAG1* polymorphisms and phenotypes in cattle. This is followed by a focus on the role of *PLAG1/PLAG1* in early embryonic development. In keeping with our earlier reviews, this review seeks to build awareness of the complex biology of embryonic development. Our consistent argument has been that a deeper understanding is needed of the factors that impact early embryo development before a meaningful transformational change can be made in the efficiency of both natural mating and assisted reproduction in cattle.

## Discovery of *PLAG1* Gene and *PLAG1* Protein

The *PLAG1* gene and *PLAG1* protein were described from 1997 to 1998 (Table 1). The seminal report showed the *PLAG1* gene to be associated with a chromosome translocation at 8q12 that was linked with pleomorphic adenomas of the salivary glands in humans (Kas et al. 1997a, b). The same laboratory described two related human proteins, *PLAGL1* and *PLAGL2*. The protein *PLAGL2* also binds to DNA and has similar properties as *PLAG1* protein (Kas et al. 1998). The *PLAG1/PLAG1* family members were subsequently assigned various names based on the association of *PLAG1* mutations with different phenotypes in different species (Table 1). In the absence of *PLAG1* gene rearrangement, and/or overexpression of *PLAG1*, *PLAG1* protein can have antiproliferative activity and tumor suppression. Hence, the regulated expression of *PLAG1* is associated with normal cellular function in different tissues, while overexpression is linked with benign tumors and malignancies (Zatkova et al., 2004). Overexpression of *PLAG1* leads to overproduction of *PLAG1*, rather than changes in the structure of *PLAG1* protein. *PLAG1* stimulates the *IGF2* gene and excess production of *IGF2* is considered one mechanism linked to tumors and cancers (Voz et al., 2000, 2004; Zatkova et al., 2004; Akhtar et al., 2012).



**Figure 1.** Zygotic genome activation in cattle. *PLAG1* is maternally imprinted and *PLAG1* protein derived from paternally expressed *PLAG1* could potentially be present in embryos from the 2 to 4 cell stage.

In humans, the *PLAG1* gene comprises 6 exons and 5 introns. *PLAG1* has yet to be fully described in cattle and is presently thought to comprise 3 introns and 4 exons (Van Dyck et al., 2007; Figure 2). In cattle, a 19-base pair inser-

tion/deletion (19-bp indel) at Exon 1, and single-nucleotide polymorphisms at Exons 3 and 4, are associated with growth, stature, and carcass traits (Karim et al. 2011; Littlejohn et al. 2011; Zhong et al., 2019; Figure 2). *PLAG1* mutations were

**Table 1.** Discovery of the pleomorphic adenoma gene (*PLAG1*) family members

Name	Function described	Year	Species	Reference
<i>PLAG1</i> : pleomorphic adenoma gene	Activation in salivary gland tumorigenesis	1997	Human	Kas et al. 1997a, b
* <i>LOT1</i> : lost-on-transformation	Decreased or lost expression in transformed ovarian epithelia cells that developed into malignant ovarian tumors	1997	Rat	Abdollahi et al. 1997a, b; see also Abdollahi 2007
* <i>ZAC</i> / <i>ZAC1</i> : zinc-finger protein found to regulate apoptosis and cell cycle arrest	Induction of apoptosis and G <sub>1</sub> cell cycle arrest and inhibition of tumor growth	1997	Mouse	Spengler et al. 1997
* <i>PLAGL1</i> : <i>PLAG1</i> like zinc-finger 1 <i>PLAGL2</i> : <i>PLAG1</i> like zinc-finger protein 2	Identified by screening mouse embryo and human fetal kidney cDNA libraries using <i>PLAG1</i> open reading frames (ORF)	1998	Human, Mouse	Kas et al. 1998

\*Same *PLAG*/*PLAG* family member.

also associated with age at puberty and circulating levels of IGF1 in heifers (Fortes et al., 2013). *PLAG1* is located within the same quantitative trait loci as the coiled-coil-helix-coiled-coil-helix domain containing 7 (*CHCHD7*) gene, which is also associated with growth and stature in several species including cattle (Li et al., 2020a; Xu et al., 2020). Both genes share the same bi-directional promoter and SNPs known to influence the transcriptional activity of the promoter impact the expression of *PLAG1* and *CHCHD7* (Karim et al., 2011; Fink et al., 2017; Figure 2). *PLAG1* protein is comprised of three regions with distinct functions: a region with nuclear translocation signals for the transfer of *PLAG1* to the nucleus; C<sub>2</sub>H<sub>2</sub>-like zinc-finger domains that interact with DNA to influence transcription; a serine-rich region that has transcriptional activation activity (Braem et al., 2002; Hensen et al., 2002; Figure 2).

### **PLAG1 and Phenotype in Cattle**

The most studied relationships between *PLAG1*/*PLAG1* and phenotype in cattle are for growth and stature (Karim et al., 2011; Pryce et al., 2011; Visscher & Goddard, 2011; Boitard et al., 2016; Takasuga, 2016; Taye et al., 2017; Utsunomiya et al., 2017; Bouwman et al., 2018). As noted above, *PLAG1* is most noticeably expressed during fetal development and *PLAG1* polymorphisms are linked with differences in birth weight and calving ease in cattle (Littlejohn et al., 2011; Pausch et al., 2011; Utsunomiya et al., 2013). *PLAG1* polymorphisms are also associated with growth, mature body size, and stature, in different breeds of cattle including Holstein-Friesian (Littlejohn et al., 2011; Zhao et al., 2015), Holstein Friesian × Jersey (Karim et al., 2011), Chinese (Xu et al., 2018; Hou et al., 2019; Zhong et al., 2019; Zhou et al., 2019; Li et al., 2020b), European (Randhawa et al., 2015; Zhao et al., 2015), African (Randhawa et al., 2015), and Japanese Black (Hoshihira et al., 2013; Sasaki et al., 2013). Other commercially important production traits in cattle linked with *PLAG1* polymorphisms are carcass weight and meat yield (Nishimura et al., 2012; Hoshihira et al., 2013; Bolormaa et al., 2015; Song et al., 2016; Hay & Roberts, 2018; Zhang et al., 2019), milk quality (Zhao et al., 2015; Fink et al., 2017), and adaptation (Porto-Neto et al., 2014; Boitard et al., 2016). *PLAG1* influences growth and production traits in goats (Wei et al., 2021) and sheep (Wu et al., 2019; Pan et al., 2022).

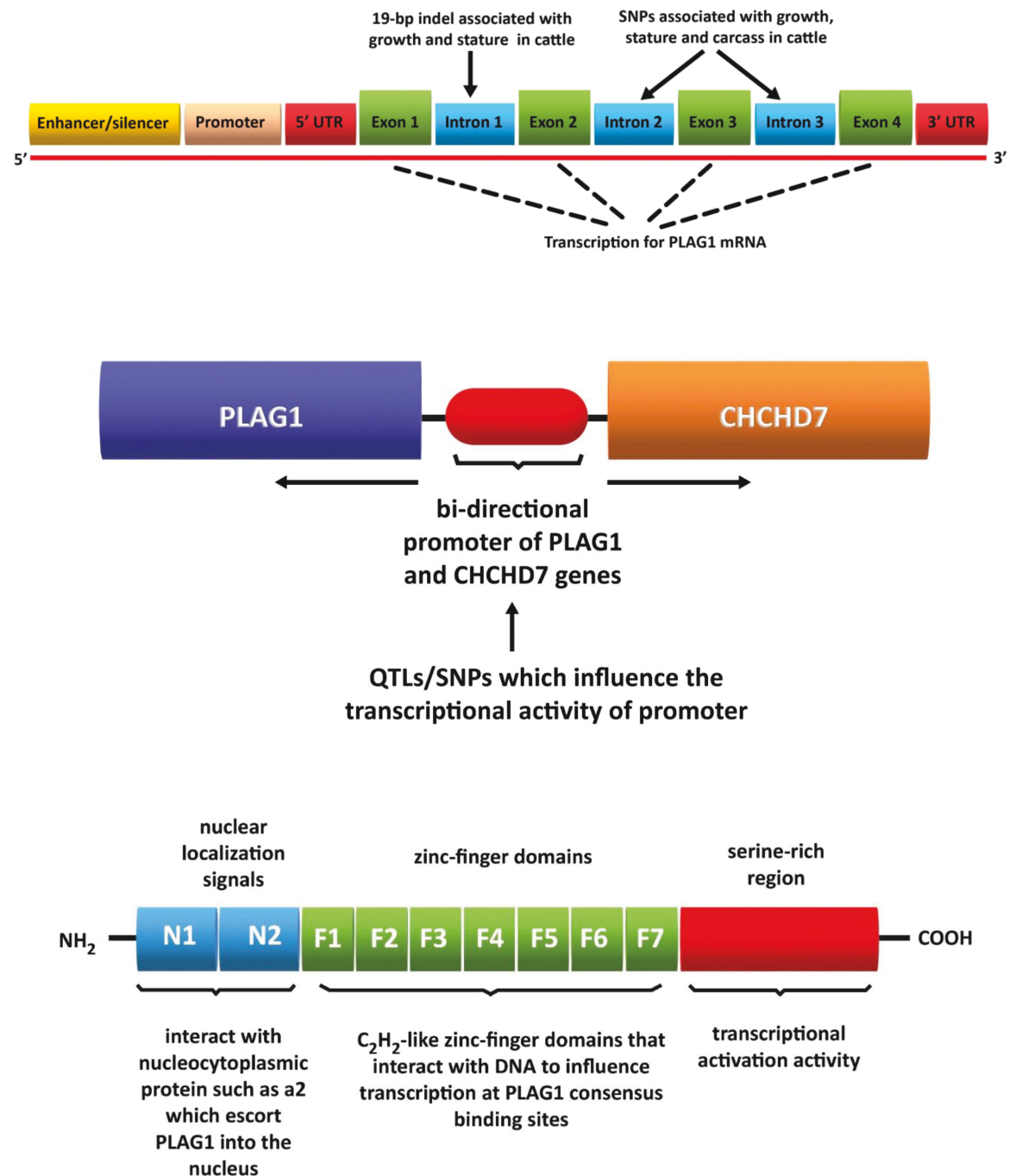
A major target for *PLAG1* protein is the *IGF2* gene and *PLAG1* binding sites are present in the promoter of *IGF2*

(Voz et al., 2000, 2004; Zatkova et al., 2004; Van Dyck et al., 2007; Akhtar et al., 2012; Wang et al., 2013). *IGF2* codes for the IGF2 protein which is an important fetal mitogen (O'Dell & Day, 1998; Curchoe et al., 2005; Berkowicz et al., 2010; Bergman et al., 2013). It is generally accepted that growth in cattle is at least partly associated with variants of *PLAG1*, and differential regulation of *IGF2* by *PLAG1* protein (Bolormaa et al., 2015). *IGF2* is produced by placental tissue and acts in both the placenta and fetus (Constância et al., 2002; Figure 3). The developing fetus likewise produces *IGF2* which acts at the fetus and placenta (Akhtar et al., 2012; Agrogiannis et al., 2014; Sandovici et al., 2022). Inactivation of *PLAG1* is associated with reduced *IGF2* and fetal growth retardation (Hensen et al., 2004; Varrault et al., 2006; Habib et al., 2018). Aberrant imprinting of *PLAG1* and overexpression is associated with the large fetus syndrome (Chen et al., 2015). Relationships between *PLAG1*, *IGF1* and phenotype have been described for cattle (Fortes et al., 2013).

### **PLAG1/PLAG1 and Reproduction**

#### **Puberty**

Age at puberty is a highly important trait which is linked to lifetime fertility in female cattle (Hawken et al., 2012; Wathes et al., 2014; D'Occhio et al., 2019a). Mutations on chromosome 14 (BTA14), in proximity to *PLAG1*, were reported to be associated with puberty in Zebu (*Bos indicus*) heifers including Brahman (Hawken et al., 2012; Fortes et al., 2013) and Nellore (Mota et al., 2020). Heifers with delayed puberty linked to various *PLAG1* mutations are heavier at puberty. Over 36 yr, we have subjected a herd of Brahman (*Bos indicus*) females to uncompromising selection for fertility (Collins Belah Valley [CBV] Brahman, Belah Valley Cattle Station, Marlborough, Central Queensland, Australia). Females remain in this herd only if they conceive, wean a calf, and reconceive in successive years starting with their first mating (Collins A. Snr., J. E. Kinder, and M. J. D'Occhio, unpublished). Days-to-calving (DTC), defined as the number of days from the start of mating to subsequent calving, is the most important measure of fertility in Brahman and the key driver of profit in beef production. Herd records are used to calculate estimates of genetic differences between animals for DTC and these are expressed as estimated breeding value (EBV) or estimated progeny difference. Female cattle with a low DTC EBV show early puberty as heifers and resume cyclic ovarian function sooner after calving. The DTC EBV



**Figure 2.** The putative structure of the *PLAG1* gene in cattle and variants of *PLAG1* associated with different phenotypes. Indel, insertion/deletion; SNPs, single-nucleotide polymorphisms (top); the common bi-directional promoter of the *PLAG1* and *CHCHD7* genes. QTLs/SNPs in the promoter influence the transcriptional activity of *PLAG1* and *CHCHD7* and phenotypes in cattle including growth and stature. QTLs, quantitative trait loci; SNPs, single-nucleotide polymorphisms (middle); and the structure of *PLAG1* protein and domains associated with translocation to the nucleus and binding to DNA. *PLAG1* typically binds to the promoter of target genes to influence transcription (bottom).

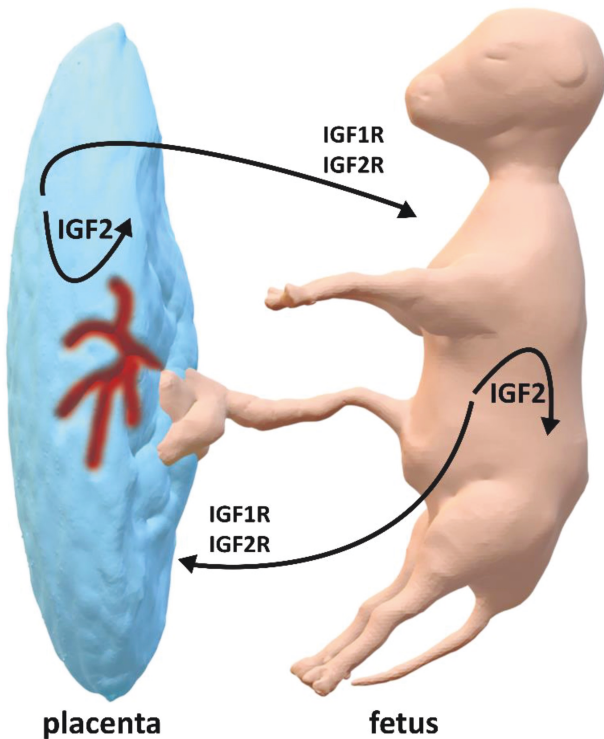
for the CBV Brahman herd is  $-16.8$  d compared with the Australian Brahman breed average DTC EBV of  $-3.2$  d. The latter demonstrates a strong genetic component for high fertility of the CBV Brahman herd. It was recently shown that maiden heifers in the CBV Brahman herd that were homozygous for the *PLAG1* variant rs109815800 (G > T) conceived earlier and had greater fertility than contemporary heifers with either one or no copies of the variant (Engle & Hayes, 2022). Heifers with two copies of the variant had a smaller

stature than heifers with one or no copies (Engle & Hayes, 2022).

### Ovarian follicles and embryonic and fetal development

In addition to an effect on age at puberty, *PLAG1/PLAG1* have been broadly associated with reproductive function in fish and mammals (Pendeville et al., 2006; Juma et al., 2016, 2017, 2018; Wong et al., 2020a, b). The relationship between

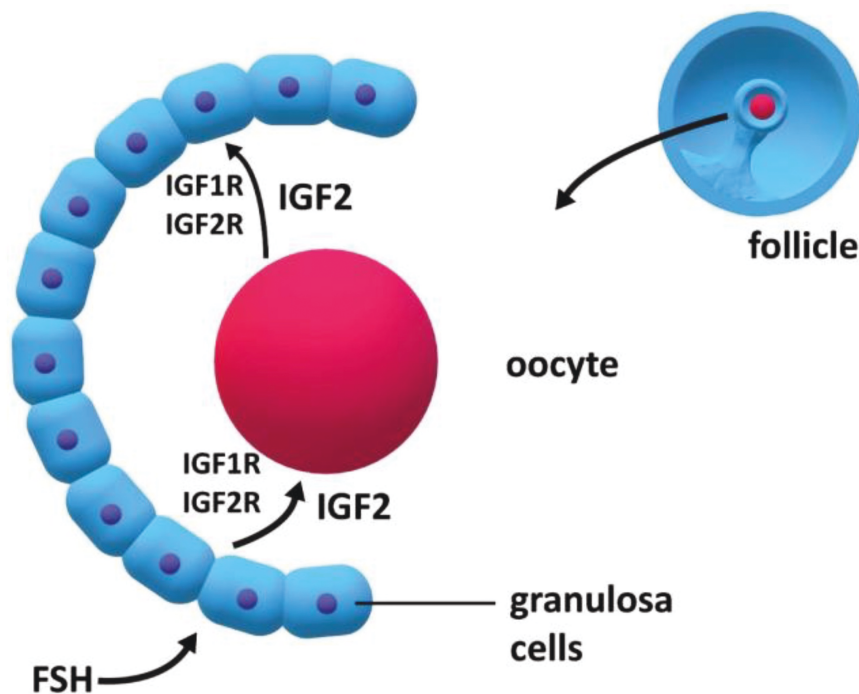
*PLAG1* and *IGF2* in growth and development, which is discussed above, can be extended to ovarian function and embryonic development in cattle (Neirijnck et al., 2019). *IGF2* is



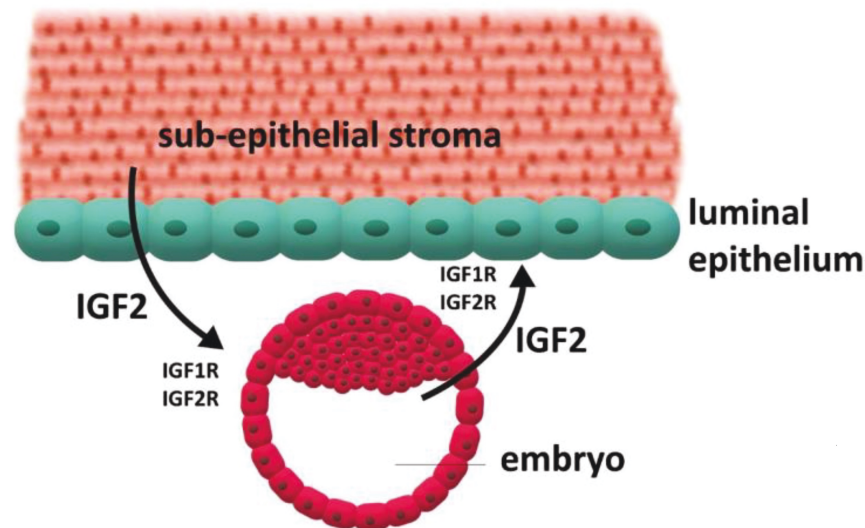
**Figure 3.** Insulin-like growth factor 2 (*IGF2*) is produced by the fetus and placenta and has both local and reciprocal action between the fetus and placenta. *IGF2* can bind to both *IGF1* and *IGF2* receptors on target cells.

expressed in growing ovarian follicles and has important mitogenic actions on both the follicle and oocyte (Hunter et al., 2004; Spicer & Aad, 2007; Brogan et al., 2010; Aad et al., 2013; Baumgarten et al., 2015; Tkachenko et al., 2021; Figure 4). Oocytes also produce *IGF2* which influences the function of oocytes and follicles (Willhelm et al., 2021; Figure 4). *IGF2* is additionally expressed by early embryos and the uterus and is involved in autocrine, paracrine, and endocrine events associated with embryonic growth, attachment, and implantation (Robinson et al., 2000; Willhelm et al., 2021; Figure 5). *IGF2* is maternally imprinted similar to *PLAG1* (DeChiara et al., 1991; Giannoukakis et al., 1993; Dindot et al., 2004; Gebert et al., 2006, 2009; Sandovici et al., 2022). As noted above, in early embryos *PLAG1* protein acts at the promoter region of over 1,000 genes including *IGF2* (Madissoon et al., 2019). Mouse embryos lacking maternal *PLAG1* transitioned slowly from the 2- to 4-cell stage of development (Madissoon et al., 2019). Embryos that transition through early cell divisions in a timely manner have a greater likelihood of surviving and establishing a pregnancy. In mice that lacked maternal *PLAG1* the gene was expressed ectopically from the paternal allele earlier than would otherwise occur (Madissoon et al., 2019).

MicroRNAs (miRNAs) have been implicated in the function of *PLAG1/PLAG1* in early development (Maccani & Marsit, 2011; Kochhar et al., 2021). For example, miRNA-141 downregulates *PLAG1* translation which is associated with fetal growth retardation (Tang et al., 2013). Based on the relationship between *PLAG1* and expression of the *IGF2* gene discussed above, it was concluded that miRNA-141 downregulation of *PLAG1* results in reduced *IGF2*, and suppressed fetal growth (Varrault et al., 2006; Tang et al., 2013; Saha et al., 2015). There is a lack of information on the specific localization of *PLAG1* expression in the embryos and uterus and this is an area that warrants investigation.



**Figure 4.** Insulin-like growth factor 2 (*IGF2*) is produced by oocytes and granulosa cells of follicles and has a local and reciprocal action in oocytes and follicles. *IGF2* is an important mitogen and can bind to both *IGF1* and *IGF2* receptors at target cells. The *IGF2* gene is influenced by *PLAG1* protein which provides a mechanism for *PLAG1* to be associated with oocyte and follicular function.



**Figure 5.** Insulin-like growth factor 2 (IGF2) is produced by the embryo and uterine stroma and has a local and reciprocal action in embryos and uterus. IGF2 is an important mitogen and can bind to both IGF1 and IGF2 receptors at target cells. The *IGF2* gene is influenced by *PLAG1* protein which provides a mechanism for *PLAG1* to be associated with embryonic and uterine function.

### **PLAG1/PLAG1 and Embryos Survival in Cattle**

As noted above, the failure of embryos to progress to implantation and pregnancy is the major cause of reproductive loss in cattle. A deeper understanding of the factors which support embryonic development, attachment, and implantation, is key to improving embryo survival and achieving a transformational increase in reproductive success in female cattle. The factors are both genetic and non-genetic, although these are clearly interrelated. As noted above, Brahman (*Bos indicus*) heifers homozygous for the *PLAG1* variant, rs109815800 (G > T), show greater fertility than contemporary heifers with either one or no copy of the variant. Greater fertility in heifers homozygous for rs109815800 could be due to an earlier age at puberty and/or an increased propensity for embryo survival. The latter would mean that homozygous heifers require fewer matings to achieve pregnancy; typical embryo loss in cattle is in the order of 40% to 60%. Another *PLAG1* variant, rs109231213, appears to be associated with central mechanisms of puberty in heifers (Fortes et al., 2013, 2016; DeAtley et al., 2018). Based on the information provided in this review, it is plausible that *PLAG1/PLAG1* have a role in embryonic development and survival in cattle. This is supported by the important roles of IGF2 in follicles/oocytes, embryos, and fetuses, and the regulation of *IGF2/IGF2* by *PLAG1*. A role in central mechanisms associated with puberty in cattle is also plausible.

Notwithstanding the body of evidence that links *PLAG1/PLAG1* with IGF2 and embryonic development and reproduction generally, it is noted that some of the relationships in this review could be considered associations and further research is needed to demonstrate additional cause-and-effect relationships.

### **Summary**

The present review has looked at the emerging roles of *PLAG1/PLAG1* in embryonic development, placentation, and fetal growth. The most notable expression of *PLAG1* occurs during embryonic and fetal development, with lesser expression after

birth. Overexpression of *PLAG1* is associated with the large calf syndrome in cattle and under-expression is linked to fetal growth restriction in cattle and humans. The overexpression of *PLAG1* later in life is typically associated with the formation of solid tumors and cancers. Hence, the expression of *PLAG1* is finely balanced, and disruption in expression at different stages in life shifts *PLAG1* from having beneficial effects to adverse outcomes. *PLAG1/PLAG1* influence the expression of the *IGF2* gene, and the IGF2 protein is an important mitogen in reproduction. The *PLAG1-IGF2* axis, therefore, provides a mechanistic basis for an effect of *PLAG1* on ovarian follicles/oocytes, embryos, and fetuses. Our own work involving the selection of Brahman (*Bos indicus*) female cattle for fertility over a period of 35 yr has led to a herd in which heifers homozygous for the *PLAG1* variant, rs109815800, have greater fertility than contemporary heifers with either one or no copy of the variant (Collins A. Snr, J. E. Kinder, B. J. Hayes, and M. J. D'Occhio, unpublished). *PLAG1/PLAG1* would therefore appear to have important roles in embryonic development and pregnancy in cattle similar to other mammals.

### **Acknowledgments**

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### **Conflict of interest statement**

Alf Collins Snr is a Brahman seedstock producer and the owner of cattle ranch Collins Belah Valley, Marlborough, Central Queensland. All other authors declare no real or perceived conflicts of interest.

### **Literature Cited**

Aad, P. Y., S. E. Echternkamp, and L. J. Spicer. 2013. Possible role of IGF2 receptors in regulating selection of 2 dominant follicles in

- cattle selected for twin ovulations and births. *Domest Anim. Endocrinol.* 45:187–195. doi: [10.1016/j.domaniend.2013.09.001](https://doi.org/10.1016/j.domaniend.2013.09.001)
- Abdollahi, A. 2007. *Lot1 (Zac1/PLAGL1)* and its family members: mechanisms and functions. *J. Cell. Physiol.* 210:16–25. doi: [10.1002/jcp.20835](https://doi.org/10.1002/jcp.20835)
- Abdollahi, A., D. Roberts, A. K. Godwin, D. C. Schultz, G. Sonoda, J. R. Testa, and T. C. Hamilton. 1997a. Identification of a zinc-finger gene at 6q25: a chromosomal region implicated in development of many solid tumors. *Oncogene* 14:1973–1979. doi: [10.1038/sj.onc.1201034](https://doi.org/10.1038/sj.onc.1201034)
- Abdollahi, A., A. K. Godwin, P. D. Miller, L. A. Getts, D. C. Schultz, T. Taguchi, J. R. Testa, and T. C. Hamilton. 1997b. Identification of a gene containing zinc-finger motifs based on lost expression in malignant transformed rat ovarian surface epithelial cells. *Cancer Res.* 57:2029–2034.
- Adhami, H. A., B. Evano, A. Le Digarcher, C. Gueydan, E. Dubois, H. Parrinello, C. Dantec, T. Bouschet, A. Varrault, and L. Journot. 2015. A systems-level approach to parental genomic imprinting: the imprinted gene network includes extracellular matrix genes and regulates cell cycle exit and differentiation. *Genet. Res.* 25:353–367. doi: [10.1101/gr.175919.114](https://doi.org/10.1101/gr.175919.114)
- Adnani, L., R. Dixit, X. Chen, A. Balakrishnan, H. Modi, Y. Touahri, C. Logan, and C. Schuurmans. 2018. *Plag1* and *Plag2* have overlapping and distinct functions in telencephalic development. *Biol. Open.* 7:bio038661. doi: [10.1242/bio.038661](https://doi.org/10.1242/bio.038661)
- Agrogiannis, G. D., S. Sifakis, E. S. Patsouris, and A. E. Konstantinidou. 2014. Insulin-like growth factors in embryonic and fetal growth and skeletal development (Review). *Mol. Med. Rep.* 10:579–584. doi: [10.3892/mmr.2014.2258](https://doi.org/10.3892/mmr.2014.2258)
- Aguilera, C., A. E. Velásquez, Y. Wong, M. A. Gutierrez-Reinoso, J. Cabezas, B. Melo-Baez, F. Castro, and L. Rodríguez-Álvarez. 2022. Preimplantation bovine embryos secrete extracellular vesicles that participate in embryo-maternal communication. *Reprod. Fertil. Dev.* 34:234–234. doi: [10.1071/rdv34n2ab1](https://doi.org/10.1071/rdv34n2ab1)
- Akhtar, M., C. Holmgren, A. Göndör, M. Vesterlund, C. Kanduri, C. Larsson, and T. J. Ekström. 2012. Cell type and context-specific function of *PLAG1* for *IGF2* P3 promoter activity. *Int. J. Oncol.* 41:1959–1966. doi: [10.3892/ijo.2012.1641](https://doi.org/10.3892/ijo.2012.1641)
- Asp, J., F. Persson, M. Kost-Alimova, and G. Stenman. 2006. CHCHD7-*PLAG1* and *TCEA1-PLAG1* gene fusions resulting from cryptic, intrachromosomal 8q rearrangements in pleomorphic salivary gland adenomas. *Genes Chromosomes Cancer.* 45:820–828. doi: [10.1002/gcc.20346](https://doi.org/10.1002/gcc.20346)
- Åström, A. K., M. L. Voz, K. Kas, E. Röjger, B. Wedell, N. Mandahl, W. Van de Ven, J. Mark, and G. Stenman. 1999. Conserved mechanism of *PLAG1* activation in salivary gland tumors with and without chromosome 8q12 abnormalities: identification of *SII* as a new fusion partner gene. *Cancer Res.* 59:918–923.
- Barlow, D. P., and M. S. Bartolomei. 2014. Genomic imprinting in mammals. *Cold Spring Harbor Pers. Biol.* 6:a018382. doi: [10.1101/cshperspect.a018382](https://doi.org/10.1101/cshperspect.a018382)
- Baumgarten, S. C., S. M. Convissar, A. M. Zamah, M. A. Fierro, N. J. Winston, B. Scoccia, and C. Stocco. 2015. FSH regulates *IGF-2* expression in human granulosa cells in an AKT-dependent manner. *J. Clin. Endocrinol. Metab.* 100:E1046–E1055. doi: [10.1210/jc.2015-1504](https://doi.org/10.1210/jc.2015-1504)
- Bergman, D., M. Halje, M. Nordin, and W. Engström. 2013. Insulin-like growth factor 2 in development and disease: a mini-review. *Gerontology* 59:240–249. doi: [10.1159/000343995](https://doi.org/10.1159/000343995)
- Berkowicz, E. W., D. A. Magee, K. M. Sikora, D. P. Berry, D. J. Howard, M. P. Mullen, R. D. Evans, C. Spillane, and D. E. MacHugh. 2010. Single nucleotide polymorphisms at the imprinted bovine insulin-like growth factor 2 (*IGF2*) locus are associated with dairy performance in Irish Holstein-Friesian cattle. *J. Dairy Res.* 78:1–8. doi: [10.1017/S0022029910000567](https://doi.org/10.1017/S0022029910000567)
- Boitard, S., M. Boussaha, A. Capitan, D. Rocha, and B. Servin. 2016. Uncovering adaptation from sequence data: lessons from genome resequencing for four cattle breeds. *Genetics* 203:433–450. doi: [10.1534/genetics.115.181594](https://doi.org/10.1534/genetics.115.181594)
- Bolormaa, S., J. E. Pryce, Y. Zhang, A. Reverter, W. Barendse, B. J. Hayes, and M. E. Goddard. 2015. Non-adaptive genetic variation in growth, carcass and fertility traits in beef cattle. *Genet. Sel. Evol.* 47:26. doi: [10.1186/s12711-015-0114-8](https://doi.org/10.1186/s12711-015-0114-8)
- Bouwman, A. C., H. D. Daetwyler, A. J. Chamberlain, C. Hurtado Ponce, M. Sargolzaei, F. Schenkel, G. Sahana, A. Govignon-Gion, S. Boitard, M. Dolezal, et al. 2018. Meta-analysis of genome-wide association studies for cattle stature identifies common genes that regulate body size in mammals. *Nat. Genet.* 50:362–367. doi: [10.1038/s41588-018-0056-5](https://doi.org/10.1038/s41588-018-0056-5)
- Braem, C. V., K. Kas, E. Meyen, M. Debiec-Rychter, W. J. M. Van de Vent, M. L. Voz. 2002. Identification of a karyopherin  $\alpha 2$  recognition site in *PLAG1*, which functions as a nuclear localization signal. *J. Biol. Chem.* 277:19673–19678. doi: [10.1074/jbc.m112112200](https://doi.org/10.1074/jbc.m112112200)
- Brogan, R. S., S. Mix, M. Puttabyatappa, C. A. Van de Voort, and C. L. Chaffin. 2010. Expression of the *IGF* and insulin systems in the luteinizing macaque ovarian follicle. *Fertil. Steril.* 93:1421–1429. doi: [10.1016/j.fertnstert.2008.12.096](https://doi.org/10.1016/j.fertnstert.2008.12.096)
- Cajas, Y. N., K. Cañon-Beltrán, M. G. M. de la Blanca, J. M. Sánchez, B. Fernandez-Fuertes, E. M. González, and D. Rizos. 2022. Role of reproductive fluids and extracellular vesicles in embryo-maternal interaction during early pregnancy in cattle. *Reprod. Fertil. Dev.* 34:117–138. doi: [10.1071/RD21275](https://doi.org/10.1071/RD21275)
- Campanile, G., P. S. Baruselli, A. Limone, and M. J. D’Occhio. 2021. Local action of cytokines and immune cells in communication between the conceptus and uterus during the critical period of early embryo development, attachment and implantation - implications for embryo survival in cattle: a review. *Theriogenology.* 167:1–12. doi: [10.1016/j.theriogenology.2021.02.020](https://doi.org/10.1016/j.theriogenology.2021.02.020)
- Chen, Z., D. E. Hagen, C. G. Elsik, T. Ji, C. J. Morris, L. E. Moon, and R. M. Rivera. 2015. Characterization of global loss of imprinting in fetal growth syndrome induced by assisted reproduction. *Proc. Natl. Acad. Sci.* 112:4618–4623. doi: [10.1073/pnas.1422088112](https://doi.org/10.1073/pnas.1422088112)
- Constância, M., M. Hemberger, J. Hughes, W. Dean, A. Ferguson-Smith, R. Fundele, F. Stewart, G. Kelsey, A. Fowden, C., Sibley, et al. 2002. Placental-specific *IGF-II* is a major modulator of placental and fetal growth. *Nature* 417:945–948. doi: [10.1038/nature00819](https://doi.org/10.1038/nature00819)
- Curchoe, C., S. Zhang, Y. Bin, X. Zhang, L. Yang, D. Feng, M. O’Neill, and X. C. Tian. 2005. Promoter-specific expression of the imprinted *IGF2* gene in cattle (*Bos taurus*). *Biol. Reprod.* 73:1275–1281. doi: [10.1095/biolreprod.105.044727](https://doi.org/10.1095/biolreprod.105.044727)
- D’Occhio, M. J., P. S. Baruselli, and G. Campanile. 2019a. Influence of nutrition, body condition and metabolic status on reproduction in female cattle: a review. *Theriogenology.* 125:277–284. doi: [10.1016/j.theriogenology.2018.11.010](https://doi.org/10.1016/j.theriogenology.2018.11.010)
- D’Occhio, M. J., G. Campanile, L. Zicarelli, J. A. Visintin, and P. S. Baruselli. 2019b. Adhesion molecules in gamete transport, fertilization, early embryonic development, and implantation – role in establishing a pregnancy in cattle: a review. *Mol. Reprod. Dev.* 87:206–222. doi: [10.1002/mrd.23312](https://doi.org/10.1002/mrd.23312)
- D’Occhio, M. J., G. Campanile, and P. S. Baruselli. 2020a. Transforming growth factor- $\beta$  superfamily and interferon- $\tau$  in ovarian function and embryo development in female cattle: a review of biology and application. *Reprod. Fertil. Dev.* 32:539–352. doi: [10.1071/rd19123](https://doi.org/10.1071/rd19123)
- D’Occhio, M. J., G. Campanile, and P. S. Baruselli. 2020b. Peripheral action of kisspeptin at reproductive tissues - role in ovarian function and embryo implantation and relevance to assisted reproductive technology in livestock: a review. *Biol. Reprod.* 103:1157–1170. doi: [10.1093/biolre/iaaa135](https://doi.org/10.1093/biolre/iaaa135)
- Dean, W., F. Santos, M. Stojkovic, V. Zakhartchenko, J. Walter, E. Wolf, and W. Reik. 2001. Conservation of methylation reprogramming in mammalian development: aberrant reprogramming in cloned embryos. *Proc. Natl. Acad. Sci. U.S.A.* 98:13734–13738. doi: [10.1073/pnas.241522698](https://doi.org/10.1073/pnas.241522698)
- DeAtley, K. L., M. L. Colgrave, A. Cánovas, G. Wijffels, R. L. Ashley, G. A. Silver, G. Rincon, J. F. Medrano, A. Islas-Trejo, M. R. S. Fortes, et al. 2018. Neuropeptide of the hypothalamus and pituitary gland of Indicine  $\times$  Taurine heifers: evidence of differential neuropeptide



- processing in the pituitary gland before and after puberty. *J. Prot. Res.* 17:1852–1865. doi: [10.1021/acs.jproteome.7b00875](https://doi.org/10.1021/acs.jproteome.7b00875)
- Debiec-Rychter, M., I. Van Valckenborgh, C. V. Broeck, A. Hagemeyer, W. J. M. Van de Ven, K. Kas, B. Van Damme, and M. L. Voz. 2001. Histologic localization of PLAG1 (pleomorphic adenoma gene 1) in pleomorphic adenoma of the salivary gland: cytogenetic evidence of common origin of phenotypically diverse cells. *Lab. Invest.* 81:1289–1291. doi: [10.1038/labinvest.3780342](https://doi.org/10.1038/labinvest.3780342)
- DeChiara, T. M., E. J. Robertson, and A. Efstratiadis. 1991. Parental imprinting of the mouse insulin-like growth factor II. *Cell* 64:849–859. doi: [10.1016/0092-8674\(91\)90513-x](https://doi.org/10.1016/0092-8674(91)90513-x)
- Declercq, J., F. Van Dyck, C. V. Braem, I. C. Van Valckenborgh, M. Voz, M. Wassef, L. Schoonjans, W. Van Damme, L. Fiette, and W. J. M. Van de Ven. 2005. Salivary gland tumors in transgenic mice with targeted PLAG1 proto-oncogene overexpression. *Can. Res.* 65:4544–4553. doi: [10.1158/0008-5472.can-04-4041](https://doi.org/10.1158/0008-5472.can-04-4041)
- Dindot, S. V., P. W. Farin, C. E. Farin, J. Romano, S. Walker, C. Long, and J. A. Piedrahita. 2004. Epigenetic and genomic imprinting analysis in nuclear transfer derived *Bos gaurus/Bos taurus* hybrid fetuses. *Biol. Reprod.* 71:470–478. doi: [10.1095/biolreprod.103.025775](https://doi.org/10.1095/biolreprod.103.025775)
- Diskin, M. G., S. M. Waters, M. H. Parr, and D. A. Kenny. 2016. Pregnancy losses in cattle: potential for improvement. *Reprod. Fertil. Dev.* 28:83–93. doi: [10.1071/RD15366](https://doi.org/10.1071/RD15366)
- Duan, J. E., Z. C. Jiang, F. Alqahtan, I. Mandolu, H. Dong, X. Zheng, S. L. Marjani, J. Chen, and X. C. Tian. 2019. Methylome dynamics of bovine gametes and *in vitro* early embryos. *Front. Genet.* 10:512. doi: [10.3389/fgene.2019.00512](https://doi.org/10.3389/fgene.2019.00512)
- Engle, B. N., and B. J. Hayes. 2022. Genetic variation in *PLAG1* is associated with early fertility in Australian Brahman cattle. *J. Anim. Sci.* 100:1–8. doi: [10.1093/jas/skac084](https://doi.org/10.1093/jas/skac084)
- Fink, T., K. Tiplady, T. Lopdell, T. Johnson, R. G. Snell, R. J. Spelman, S. R. Davis, and M. D. Littlejohn. 2017. Functional confirmation of *PLAG1* as the candidate causative gene underlying major pleiotropic effects on body weight and milk characteristics. *Sci. Rep.* 7:44793. doi: [10.1038/srep44793](https://doi.org/10.1038/srep44793)
- Fortes, M. R. S., K. Kemper, S. Sasazaki, A. Reverter, J. E. Pryce, W. Barendse, R. Bunch, R. McCulloch, B. Harrison, S. Bolormaa, et al. 2013. Evidence for pleiotropism and recent selection in the *PLAG1* region in Australian beef cattle. *Anim. Genet.* 44:636–647. doi: [10.1111/age.12075](https://doi.org/10.1111/age.12075)
- Fortes, M. R. S., L. T. Nguyen, L. R. P. Neto, A. Reverter, S. S. Moore, S. A. Lehnert, and M. G. Thomas. 2016. Polymorphisms and genes associated with puberty in heifers. *Theriogenology.* 86:333–339. doi: [10.1016/j.theriogenology.2016.04.046](https://doi.org/10.1016/j.theriogenology.2016.04.046)
- Gabory, A., M. A. Ripoché, A. Le Digarcher, F. Watrin, A. Ziyat, T. Forné, H. Jammes, J. F. X. Ainscough, M. A. Surani, L. Journot, et al. 2009. *H19* acts as a trans regulator of the imprinted gene network controlling growth in mice. *Development* 136:3413–3421. doi: [10.1242/dev.036061](https://doi.org/10.1242/dev.036061)
- Gad, A., M. Hoelker, U. Besenfelder, V. Havlicek, U. Cinar, F. Rings, E. Held, I. Dufort, M. A. Sirard, K. Schellander, et al. 2012. Molecular mechanisms and pathways involved in bovine embryonic genome activation and their regulation by alternative *in vivo* and *in vitro* culture conditions. *Biol. Reprod.* 87:1–13. doi: [10.1095/biolreprod.112.099697](https://doi.org/10.1095/biolreprod.112.099697)
- Gebert, C., C. Wrenzycki, D. Herrmann, D. Gröger, R. Reinhardt, P. Hajkova, A. Lucas-Hahn, J. Carnwath, H. Lehrach, and H. Niemann. 2006. The bovine *IGF2* gene is differentially methylated in oocyte and sperm DNA. *Genomics* 88:222–229. doi: [10.1016/j.ygeno.2006.03.011](https://doi.org/10.1016/j.ygeno.2006.03.011)
- Gebert, C., C. Wrenzycki, D. Herrmann, D. Gröger, J. Thiel, R. Reinhardt, H. Lehrach, P. Hajkova, A. Lucas-Hahn, J. W. Carnwath, et al. 2009. DNA methylation in the *IGF2* intragenic DMR is re-established in a sex-specific manner in bovine blastocysts after somatic cloning. *Genomics* 94:63–69. doi: [10.1016/j.ygeno.2009.03.004](https://doi.org/10.1016/j.ygeno.2009.03.004)
- Giannoukakis, N., C. Deal, J. Paquette, C. G. Goodyer, and C. Polychronakos. 1993. Parental genomic imprinting of the human *IGF2* gene. *Nat. Genet.* 4:98–101. doi: [10.1038/ng0593-98](https://doi.org/10.1038/ng0593-98)
- Graf, A., S. Krebs, M. Heininen-Brown, V. Zakhartchenko, H. Blum, and E. Wolf. 2014a. Genome activation in bovine embryos: review of the literature and new insights from RNA sequencing experiments. *Anim. Reprod. Sci.* 149:46–58. doi: [10.1016/j.anireprosci.2014.05.016](https://doi.org/10.1016/j.anireprosci.2014.05.016)
- Graf, A., S. Krebs, V. Zakhartchenko, B. Schwalb, H. Blum, and E. Wolf. 2014b. Fine mapping of genome activation in bovine embryos by RNA sequencing. *Proc. Natl. Acad. Sci. U.S.A.* 111:4139–4144. doi: [10.1073/pnas.1321569111](https://doi.org/10.1073/pnas.1321569111)
- Guzeloglu-Kayisli, O., U. A. Kayisli, and H. S. Taylor. 2009. The role of growth factors and cytokines during implantation: endocrine and paracrine interactions. *Semin. Reprod. Med.* 27:62–79. doi: [10.1055/s-0028-1108011](https://doi.org/10.1055/s-0028-1108011)
- Habib, W. A., F. Brioude, T. Edouard, J. T. Bennett, A. Lienhardt-Roussie, F. Tixier, J. Salem, T. Yuen, S. Azzi, Y. Le Bouc, et al. 2018. Genetic disruption of the oncogenic *HMG2-PLAG1-IGF2* pathway causes fetal growth restriction. *Genet. Med.* 20:250–258. doi: [10.1038/gim.2017.105](https://doi.org/10.1038/gim.2017.105)
- Halstead, M. M., X. Ma, C. Zhou, R. M. Schultz, and P. J. Ross. 2020. Chromatin remodeling in bovine embryos indicates species-specific regulation of genome activation. *Nat. Commun.* 11:4654. doi: [10.1038/s41467-020-18508-3](https://doi.org/10.1038/s41467-020-18508-3)
- Han, D. W., S. J. Song, J. Uhum, J. T. Do, N. H. Kim, K. S. Chung, and H. T. Lee. 2003. Expression of *IGF2* and *IGF* receptor mRNA in bovine nuclear transferred embryos. *Zygote* 11:245–252. doi: [10.1017/s0967199403002296](https://doi.org/10.1017/s0967199403002296)
- Hansen, P. J. 2020. The incompletely fulfilled promise of embryo transfer in cattle – why aren't pregnancy rates greater and what can we do about it? *J. Anim. Sci.* 98:1–20. doi: [10.1093/jas/skaa288](https://doi.org/10.1093/jas/skaa288)
- Hantak, A. M., I. C. Bagchi, and M. K. Bagchi. 2014. Role of uterine stromal-epithelial crosstalk in embryo implantation. *International J. Dev. Biol.* 58:139–146. doi: [10.1387/ijdb.130348mb](https://doi.org/10.1387/ijdb.130348mb)
- Hawken, R. J., J. D. Zhang, M. R. S. Fortes, E. Collis, W. C. Barris, N. J. Corbet, P. J. Williams, G. Fordyce, R. G. Holroyd, J. R. W. Walkley, et al. 2012. Genome-wide association studies of female reproduction in tropically adapted beef cattle. *J. Anim. Sci.* 90:1398–1410. doi: [10.2527/jas.2011-4410](https://doi.org/10.2527/jas.2011-4410)
- Hay, E. H., and A. Roberts. 2018. Genome-wide association study for carcass traits in a composite beef cattle. *Liv. Sci.* 213:35–43. doi: [10.1016/j.livsci.2018.04.018](https://doi.org/10.1016/j.livsci.2018.04.018)
- Hensen, K., I. C. C. Van Valckenborgh, K. Kas, W. J. M. Van de Ven, and M. L. Voz. 2002. The tumorigenic diversity of the three *PLAG* family members is associated with different DNA binding capacities. *Can. Res.* 62:1510–1617.
- Hensen, K., C. Braem, J. Declercq, F. Van Dyck, M. Dewerchin, L. Fiette, C. Denef, and W. J. M. Van de Ven. 2004. Targeted disruption of the murine *Plag1* proto-oncogene causes growth and reduced fertility. *Dev. Growth Differ.* 46:459–470. doi: [10.1111/j.1440-169x.2004.00762.x](https://doi.org/10.1111/j.1440-169x.2004.00762.x)
- Hoshiba, H., K. Setoguchi, T. Watanabe, A. Kinoshita, K. Mizoshita, Y. Sugimoto, and A. Takasuga. 2013. Comparison of the effects explained by variation in the bovine *PLAG1* and *NCAPG* genes on the daily body weight gain, linear skeletal measurements and carcass traits in Japanese Black steers from a progeny testing program. *Anim. Sci. J.* 84:529–534. doi: [10.1111/asj.12033](https://doi.org/10.1111/asj.12033)
- Hou, J., K. Qu, P. Jia, Q. Hanif, J. Zhang, N. Chen, R. Dang, H. Chen, B. Huang, and C. Lei. 2019. A SNP in *PLAG1* is associated with body height trait in Chinese cattle. *Anim. Genet.* 51:87–90. doi: [10.1111/age.12872](https://doi.org/10.1111/age.12872)
- Hunter, M. G., R. S. Robinson, G. E. Mann, and R. Webb. 2004. Endocrine and paracrine control of follicular development and ovulation rate in farm animals. *Anim. Reprod. Sci.* 82–83:461–477. doi: [10.1016/j.anireprosci.2004.05.013](https://doi.org/10.1016/j.anireprosci.2004.05.013)
- Ivanova, E., S. Canovas, S. Garcia-Martinez, R. Romar, J. S. Lopes, D. Rizos, M. J. Sanchez-Calabuig, F. Krueger, S. Andrews, F. Perez-Sanz, et al. 2020. DNA methylation changes during preimplantation development reveals interspecies differences and reprogramming events at imprinted genes. *Clin. Epigenetics.* 12:64. doi: [10.1186/s13148-020-00857-x](https://doi.org/10.1186/s13148-020-00857-x)

- Jiang, Z., H. Dong, X. Zheng, S. L. Marjani, D. M. Donovan, J. Chen, and X. C. Tian. 2015. mRNA levels of imprinted genes in bovine *in vivo* oocytes, embryos and cross-species comparisons with humans, mice and pigs. *Sci. Rep.* 5:17898. doi: [10.1038/srep17898](https://doi.org/10.1038/srep17898)
- Jiang, Z., J. Lin, H. Dong, X. Zheng, S. L. Marjani, J. Duan, Z. Ouyang, J. Chen, and X. C. Tian. 2018. DNA methylomes of bovine gametes and *in vivo* produced preimplantation embryos. *Biol. Reprod.* 99:949–959. doi: [10.1093/biolre/iy138](https://doi.org/10.1093/biolre/iy138)
- Jukam, D., A. M. Shariati, and J. M. Skotheim. 2017. Zygotic genome activation in vertebrates. *Dev. Cell* 42:316–332. doi: [10.1016/j.devcel.2017.07.026](https://doi.org/10.1016/j.devcel.2017.07.026)
- Juma, A. R., P. E. Damdimopoulou, S. V. H. Grommen, W. J. M. Van de Ven, and B. De Groef. 2016. Emerging role of PLAG1 as a regulator of growth and reproduction. *J. Endocrinol.* 228:R45–R56. doi: [10.1530/joe-15-0449](https://doi.org/10.1530/joe-15-0449)
- Juma, A. R., S. V. H. Grommen, M. K. O'Bryan, A. E. O'Connor, D. J. Merriner, N. E. Hall, S. R. Doyle, P. E. Damdimopoulou, D. Barriga, A. H. Hart, et al. 2017. PLAG1 deficiency impairs spermatogenesis and sperm motility in mice. *Sci. Rep.* 7:5317. doi: [10.1038/s41598-017-05676-4](https://doi.org/10.1038/s41598-017-05676-4)
- Juma, A. R., N. E. Hall, J. Wong, J. G. Gasperoni, Y. Watanabe, A. Sahota, P. E. Damdimopoulou, S. V. H. Grommen, and B. De Groef. 2018. PLAG1 expression and target genes in the hypothalamo-pituitary system in male mice. *Mol. Cell. Endocrinol.* 478:77–83. doi: [10.1016/j.mce.2018.07.009](https://doi.org/10.1016/j.mce.2018.07.009)
- Kaňka, J., A. Bryova, V. Duranthon, J. F. Oudin, N. Peynot, and J. P. Renard. 2003. Identification of differentially expressed mRNAs in bovine preimplantation embryos. *Zygote* 11:43–52. doi: [10.1017/s0967199403001060](https://doi.org/10.1017/s0967199403001060)
- Karim, L., H. Takeda, L. Lin, T. Druet, J. A. C. Arias, D. Baurain, N. Cambisano, S. R. Davis, F. Farnir, B. Grisart, et al. 2011. Variants modulating the expression of a chromosomal domain encompassing *PLAG1* influence bovine stature. *Nat. Genet.* 43:405–413. doi: [10.1038/ng.814](https://doi.org/10.1038/ng.814)
- Kas, K., E. Roijer, M. Voz, E. Meyen, G. Stenman, and W. J. M. Van de Ven. 1997a. A 2-Mb YAC contig and physical map covering the chromosome 8q12 breakpoint cluster region in pleomorphic adenomas of the salivary glands. *Genomics* 43:349–358. doi: [10.1006/geno.1997.4819](https://doi.org/10.1006/geno.1997.4819)
- Kas, K., M. L. Voz, E. Röijer, A. K. Åström, E. Meyen, G. Stenman, and W. J. M. Van de Ven. 1997b. Promoter swapping between the genes for a novel zing finger protein and  $\beta$ -catenin in pleomorphic adenomas with t(3;8)(p21;q12) translocations. *Nat. Genet.* 15:170–174. doi: [10.1038/ng0297-170](https://doi.org/10.1038/ng0297-170)
- Kas, K., M. L. Voz, K. Hensen, E. Meyen, and W. J. M. Van de Ven. 1998. Transcriptional activation capacity of the novel PLAG family of zinc finger proteins. *J. Biol. Chem.* 273:23026–23032. doi: [10.1074/jbc.273.36.23026](https://doi.org/10.1074/jbc.273.36.23026)
- Kochhar, P., M. Vukku, R. Rajashekhar, and A. Mukhopadhyay. 2021. microRNA signatures associated with fetal growth restrictions: a systematic review. *Eur. J. Clin. Nutr.* 76:1088–1102. doi: [10.1038/s41430-021-01041-x](https://doi.org/10.1038/s41430-021-01041-x)
- Lafontaine, S., R. Labrecque, J. M. Palomino, P. Blondin, and M. A. Sirard. 2020. Specific imprinted genes demethylation in association with oocyte donor's age and culture conditions in bovine embryos assessed at day 7 and 12 post insemination. *Theriogenology.* 158:321–330. doi: [10.1016/j.theriogenology.2020.09.027](https://doi.org/10.1016/j.theriogenology.2020.09.027)
- Lavagi, I., S. Krebs, K. Simmet, A. Beck, V. Zakhartchenko, E. Wolf, and H. Blum. 2018. Single-cell RNA sequencing reveals developmental heterogeneity of blastomeres during major genome activation in bovine embryos. *Sci. Rep.* 8:4071. doi: [10.1038/s41598-018-22248-2](https://doi.org/10.1038/s41598-018-22248-2)
- Li, H., X. Wang, H. Chen, L. Qu, and X. Lan. 2020a. A 17-bpInDel(rs668420586) within goat *CHCHD7* gene located in the growth-related *QTL* affecting body measurement traits. *3 Biotech.* 10:441. doi: [10.1007/s13205-020-02434-8](https://doi.org/10.1007/s13205-020-02434-8)
- Li, Z., M. Wu, H. Zhao, L. Fan, Y. Zhang, T. Yuan, S. He, P. Wang, Y. Zhang, X. Sun, et al. 2020b. The *PLAG1* mRNA expression analysis among genetic variants and relevance to growth traits in Chinese cattle. *Anim. Biotechnol.* 31:504–511. doi: [10.1080/10495398.2019.1632207](https://doi.org/10.1080/10495398.2019.1632207)
- Littlejohn, M., T. Grala, K. Sanders, C. Walker, G. Waghorn, K. Macdonald, W. Coppieters, M. Georges, R. Spelman, E. Hillerton, et al. 2011. Genetic variation in *PLAG1* associates with early life body weight and peripubertal weight and growth in *Bos taurus*. *Anim. Genet.* 43:591–594. doi: [10.1111/j.1365-2052.2011.02293.x](https://doi.org/10.1111/j.1365-2052.2011.02293.x)
- Liu, J., Q. Xiao, J. Xiao, C. Niu, Y. Li, X. Zhang, Z. Zhou, G. Shu, and G. Yin. 2022. Wnt/ $\beta$ -catenin signalling: function, biological mechanisms, and therapeutic opportunities. *Signal Transduct. Target. Ther.* 7:3. doi: [10.1038/s41392-021-00762-6](https://doi.org/10.1038/s41392-021-00762-6)
- Llobat, L. 2021. Pluripotency and growth factors in early embryonic development of mammals: a comparative approach. *Vet. Sci.* 8:78. doi: [10.3390/vetsci8050078](https://doi.org/10.3390/vetsci8050078)
- Lockhart, K. N., J. N. Drum, A. Z. Balboula, C. M. Spinka, T. E. Spencer, and M. S. Ortega. 2023. Sire modulates developmental kinetics and transcriptome of bovine embryo. *Reproduction.* 166:337–348. doi: [10.1530/REP-23-0030](https://doi.org/10.1530/REP-23-0030)
- Maccani, M. A., and C. J. Marsit. 2011. Exposure and fetal growth-associated miRNA alterations in the human placenta. *Clin Epigenetics.* 2:401–404. doi: [10.1007/s13148-011-0046-2](https://doi.org/10.1007/s13148-011-0046-2)
- Madisson, E., A. Damdimopoulos, S. Katayama, K. Krjutškov, E. Einarsdottir, K. Mamia, B. De Groef, O. Hovatta, J. Kere, and P. Damdimopoulou. 2019. Pleomorphic adenoma gene 1 is needed for timely zygotic genome activation and early embryo development. *Sci. Rep.* 9:8411. doi: [10.1038/s41598-019-44882-0](https://doi.org/10.1038/s41598-019-44882-0)
- Matsuyama, A., M. Hisaoka, and H. Hashimoto. 2011. PLAG1 expression in cutaneous mixed tumors: an immunohistochemical and molecular genetic study. *Virchows Arch.* 459:539–545. doi: [10.1007/s00428-011-1149-z](https://doi.org/10.1007/s00428-011-1149-z)
- Meirelles, F. V., A. R. Caetano, Y. F. Wantanabe, P. Ripamonte, S. F. Carambula, G. K. Merighe, and S. M. Garcia. 2004. Genome activation and developmental block in bovine embryos. *Anim. Reprod. Sci.* 8:13–20. doi: [10.1016/j.anireprosci.2004.05.012](https://doi.org/10.1016/j.anireprosci.2004.05.012)
- Memili, E., and N. L. First. 1999. Control of gene expression at the onset of bovine embryonic development. *Biol. Reprod.* 61:1198–1207. doi: [10.1095/biolreprod61.5.1198](https://doi.org/10.1095/biolreprod61.5.1198)
- Memili, E., and N. L. First. 2000. Zygotic and embryonic gene expression in cow: a review of timing and mechanisms of early gene expression as compared with other species. *Zygote* 8:87–96. doi: [10.1017/s0967199400000861](https://doi.org/10.1017/s0967199400000861)
- Memili, E., T. Dominko, and N. L. First. 1998. Onset of transcription in bovine oocytes and preimplantation embryos. *Mol. Reprod. Dev.* 51:36–41. doi: [10.1002/\(SICI\)1098-2795\(199809\)51:1<36::AID-MRD4>3.0.CO;2-X](https://doi.org/10.1002/(SICI)1098-2795(199809)51:1<36::AID-MRD4>3.0.CO;2-X)
- Moore, T., and D. Haig. 1991. Genomic imprinting in mammalian development: a parental tug-of-war. *Trends Genet.* 7:45–49. doi: [10.1016/0168-9525\(91\)90230-N](https://doi.org/10.1016/0168-9525(91)90230-N)
- Mota, L. F. M., F. B. Lopes, G. A. F. Júnior, G. J. M. Rosa, A. F. B. Magalhães, R. Carvalheiro, and L. G. Albuquerque. 2020. Genome-wide scan highlights the role of candidate genes on phenotypic plasticity for age at first calving in Nellore heifers. *Sci. Rep.* 10:6481. doi: [10.1038/s41598-020-63516-4](https://doi.org/10.1038/s41598-020-63516-4)
- Namiki, T., J. Terakawa, H. Karakama, M. Noguchi, H. Murakami, Y. Hasegawa, O. Ohara, T. Daikoku, J. Ito, and N. Kashiwazaki. 2023. Uterine epithelial Gp130 orchestrates hormone response and epithelial remodeling for successful embryo attachment in mice. *Sci. Rep.* 13:854. doi: [10.1038/s41598-023-27859-y](https://doi.org/10.1038/s41598-023-27859-y)
- Neirijnck, Y., M. D. Ppaioannou, and S. Nef. 2019. The insulin/IGF system in mammalian sexual development and reproduction. *Int. J. Mol. Sci.* 20:4440. doi: [10.3390/ijms20184440](https://doi.org/10.3390/ijms20184440)
- Niemann, H., and C. Wrenzycki. 1999. Alterations of expression of developmentally important genes in preimplantation bovine embryos by *in vitro* culture conditions: implications for subsequent development. *Theriogenology.* 53:21–34. doi: [10.1016/s0093-691x\(99\)00237-x](https://doi.org/10.1016/s0093-691x(99)00237-x)
- Nishimura, S., T. Watanabe, K. Mizoshita, K. Tatsuda, T. Fujita, N. Watanabe, Y. Sugimoto, and A. Takasuga. 2012. Genome-wide association study identified three major *QTL* for carcass weight

- including the *PLAG1-CHCHD7* QTN for stature in Japanese Black cattle. *BMC Genet.* 13:40. doi: [10.1186/1471-2156-13-40](https://doi.org/10.1186/1471-2156-13-40)
- O'Dell, S. D., and I. N. M. Day. 1998. Molecules in focus insulin-like growth factor II (IGF-II). *Int. J. Biochem. Cell Biol.* 30:767–771. doi: [10.1016/S1357-2725\(98\)00048-X](https://doi.org/10.1016/S1357-2725(98)00048-X)
- O'Doherty, A. M., L. C. O'Shea, and T. Fair. 2012. Bovine DNA methylation imprints are established in an oocyte size-specific manner, which are coordinated with the expression of the DNMT3 family proteins. *Biol. Reprod.* 86:1–10. doi: [10.1095/biolreprod.111.094946](https://doi.org/10.1095/biolreprod.111.094946)
- O'Doherty, A. M., D. A. Magee, L. C. O'Shea, N. Forde, M. E. Beltram, S. Mamo, and T. Fair. 2015. DNA methylation dynamics at imprinted genes during bovine pre-implantation embryo development. *BMC Dev. Biol.* 15:13. doi: [10.1186/s12861-015-0060-2](https://doi.org/10.1186/s12861-015-0060-2)
- Ozawa, M., M. Sakatani, J. Q. Yao, S. Shanker, F. Yu, R. Yamashita, S. Wakabayashi, K. Nakai, K. B. Dobbs, M. J. Sudano, et al. 2012. Global gene expression of the inner cell mass and trophectoderm of the bovine blastocyst. *BMC Dev. Biol.* 12:33. doi: [10.1186/1471-213x-12-33](https://doi.org/10.1186/1471-213x-12-33)
- Pan, Y., M. Wang, H. Wu, Z. Akhatayeva, X. Lan, P. Fei, C. Mao, and F. Jiang. 2022. Indel mutations of sheep *PLAG1* gene and their associations with growth traits. *Anim. Biotechnol.* 33:1459–1465. doi: [10.1080/10495398.2021.1906265](https://doi.org/10.1080/10495398.2021.1906265)
- Pausch, H., K. Flisikowski, S. Jung, R. Emmerling, C. Edel, K. U. Götz, and R. Fries. 2011. Genome-wide association study identifies two major loci affecting calving ease and growth-related traits in cattle. *Genetics* 187:289–297. doi: [10.1534/genetics.110.124057](https://doi.org/10.1534/genetics.110.124057)
- Pendeville, H., B. Peers, K. Kas, and M. L. Voz. 2006. Cloning and embryonic expression of zebrafish *PLAG* genes. *Gene Expr. Patterns* 6:267–276. doi: [10.1016/j.modgep.2005.08.001](https://doi.org/10.1016/j.modgep.2005.08.001)
- Plasschaert, R. N., and M. S. Bartolomei. 2014. Genomic imprinting in development, growth, behavior and stem cells. *Development* 141:1805–1813. doi:[10.1242/dev.101428](https://doi.org/10.1242/dev.101428)
- Porto-Neto, L. R., A. Reverter, K. C. Prayaga, E. K. F. Chan, D. J. Johnston, R. J. Hawken, G. Fordyce, J. F. Garcia, T. S. Sonstegard, S. Bolormaa, et al. 2014. The genetic architecture of climatic adaptation of tropical cattle. *PLoS One* 9:e113284. doi: [10.1371/journal.pone.0113284](https://doi.org/10.1371/journal.pone.0113284)
- Pryce, J. E., B. J. Hayes, S. Bolormaa, and M. E. Goddard. 2011. Polymorphic regions affecting human height also control stature in cattle. *Genetics* 187:981–984. doi: [10.1534/genetics.110.123943](https://doi.org/10.1534/genetics.110.123943)
- Randhawa, I. A. S., M. S. Khatkar, P. C. Thomson, and H. W. Raadsma. 2015. Composite selection signals for complex traits exemplified through bovine stature using multibreed cohorts of European and African *Bos taurus*. *G3 (Bethesda)*. 5:1391–1401. doi: [10.1534/g3.115.017772](https://doi.org/10.1534/g3.115.017772)
- Rizos, D., V. Maillou, M. J. Sánchez-Calabuig, and P. Lonergan. 2017. The consequences of maternal-embryonic cross talk during the periconception period on subsequent embryonic development. *Adv. Exp. Med. Biol.* 1014:69–86. doi: [10.1007/978-3-319-62414-3\\_4](https://doi.org/10.1007/978-3-319-62414-3_4)
- Robertson, S. A., P. Y. Chin, J. G. Femia, and H. M. Brown. 2018. Embryonic cytokines – potential loss in embryo loss and fetal programming. *J. Reprod. Immunol.* 125:80–88. doi: [10.1016/j.jri.2017.12.003](https://doi.org/10.1016/j.jri.2017.12.003)
- Robinson, R. S., G. E. Mann, T. S. Gadd, G. E. Lamming, and D. C. Wathes. 2000. The expression of the IGF system in the bovine uterus throughout the oestrous cycle and early pregnancy. *J. Endocrinol.* 165:231–243. doi: [10.1677/joe.0.1650231](https://doi.org/10.1677/joe.0.1650231)
- Binelli, M., F. A. C. C. Silva, C. C. Rocha, T. Martins, M. Sponchiado, V. Van Hoeck, A. Cordeiro, M. Campbell, J. L. M. R. Leroy, F. Peñagaricano, et al. 2022. Endometrial receptivity in cattle: the mutual reprogramming paradigm. *Anim. Biotechnol.* 19:e20220097. doi: [10.1590/1984-3143-AR2022-0097](https://doi.org/10.1590/1984-3143-AR2022-0097)
- Ruddock, N. T., K. J. Wilson, M. A. Cooney, N. A. Korfiatis, R. T. Tecirlioglu, and A. J. French. 2004. Analysis of imprinted messenger RNA expression during bovine preimplantation development. *Biol. Reprod.* 70:1131–1135. doi: [10.1095/biolreprod.103.022236](https://doi.org/10.1095/biolreprod.103.022236)
- Saha, S., J. Choudhury, and R. Ain. 2015. MicroRNA-141-3p and miR-200a-3p regulate insulin-like growth factor 2 during mouse placental development. *Mol. Cell. Endocrinol.* 414:186–193. doi: [10.1016/j.mce.2015.07.030](https://doi.org/10.1016/j.mce.2015.07.030)
- Sakai, H., Y. Fujii, N. Kuwayama, K. Kawaji, Y. Gotoh, and Y. Kishi. 2019. *Plag1* regulates neuronal expression and neuronal differentiation of neocortical neuronal progenitor cells. *Genes Cells.* 24:650–666. doi: [10.1111/gtc.12718](https://doi.org/10.1111/gtc.12718)
- Sandovici, I., A. Georgopoulou, V. Pérez-Garcá, A. Hufnagel, J. López-Tello, B. Y. H. Lam, S. N. Schiefer, C. Gaudreau, F. Santos, K. Hoelle, et al. 2022. The imprinted *Igf2-Igf2r* axis is critical for matching placental microvasculature expansion to fetal growth. *Dev. Cell* 57:63–79. doi: [10.1016/j.devcel.2021.12.005](https://doi.org/10.1016/j.devcel.2021.12.005)
- Sasaki, S., T. Ibi, T. Wantanabe, T. Matsuhashi, S. Ikeda, and Y. Sugimoto. 2013. Variants of the 3' UTR of *general transcription factor III $\beta$  polypeptide 2* affect female calving efficiency in Japanese Black cattle. *BMC Genet.* 14:41. doi: [10.1186/1471-2156-14-41](https://doi.org/10.1186/1471-2156-14-41)
- Sferruzzi-Perri, A. N., I. Sandovici, M. Constancia, and A. L. Fowden. 2017. Placental phenotype and the insulin-like growth factors: resource allocation to fetal growth. *J. Physiol.* 595:5057–5093. doi: [10.1113/jp273330](https://doi.org/10.1113/jp273330)
- Skálová, A., A. Agaimy, T. Vaneczek, M. Baněčková, J. Laco, N. Ptáková, P. Šteiner, H. Majewska, W. Biernat, L. Corcione, et al. 2021. Molecular profiling of clear cell myoepithelial carcinoma of salivary glands with *EWSR1* rearrangement identifies frequent *PLAG1* gene fusions but no *EWSR1* fusion transcripts. *Am. J. Surg. Pathol.* 45:1–13. doi: [10.1097/PAS.0000000000001591](https://doi.org/10.1097/PAS.0000000000001591)
- Smith, L. C., J. Therrien, F. Fillion, F. Bressan, and F. V. Meirelles. 2015. Epigenetic consequences of artificial reproductive technologies to the bovine imprinted genes *SNRPN*, *H19/IGF2*, and *IGF2R*. *Front. Genet.* 6:58. doi: [10.3389/fgene.2015.00058](https://doi.org/10.3389/fgene.2015.00058)
- Song, Y., L. Xu, Y. Chen, L. Zhang, H. Gao, B. Zhu, H. Niu, W. Zhang, J. Xia, X. Gao, et al. 2016. Genome-wide association study reveals the *PLAG1* gene for knuckle, biceps and shank weight in Simmental beef cattle. *PLoS One* 11:e0168316. doi: [10.1371/journal.pone.0168316](https://doi.org/10.1371/journal.pone.0168316)
- Spengler, D., M. Villalba, A. Hoffmann, C. Pantaloni, S. Houssami, J. Bockaert, and L. Journot. 1997. Regulation of apoptosis and cell cycle arrest by *Zac1*, a novel zinc finger protein expressed in the pituitary gland and the brain. *EMBO J.* 16:2814–2825. doi: [10.1093/emboj/16.10.2814](https://doi.org/10.1093/emboj/16.10.2814)
- Spicer, L. J., and P. Y. Aad. 2007. Insulin-like growth factor (IGF) 2 stimulates steroidogenesis and mitosis of bovine granulosa cells through the IGF1 receptor: role of follicle-stimulating hormone and IGF2 receptor. *Biol. Reprod.* 77:18–27. doi: [10.1095/biolreprod.106.058230](https://doi.org/10.1095/biolreprod.106.058230)
- Sponchiado, M., N. S. Gomes, P. K. Fonyes, T. Martins, M. Collado, A. A. Pastore, G. Pugliesi, M. F. G. Nogueira, and M. Binelli. 2017. Pre-hatching embryo-dependent and -independent programming of endometrial function in cattle. *PLoS One* 12:e017954. doi: [10.1371/journal.pone.0175954](https://doi.org/10.1371/journal.pone.0175954)
- Sponchiado, M., A. M. Gonella-Diaza, C. C. Rocha, E. G. Lo Turco, G. Pugliesi, J. L. M. R. Leroy, and M. Binelli. 2019. The pre-hatching bovine embryo transforms the uterine luminal metabolite composition *in vivo*. 2019. *Sci. Rep.* 9:8354. doi: [10.1038/s41598-019-44590-9](https://doi.org/10.1038/s41598-019-44590-9)
- Sponchiado, M., W. F. A. Marei, G. T. S. Beemster, P. E. J. Bols, M. Binelli, and J. L. M. R. Leroy. 2020. Molecular interactions at the bovine embryo-endometrial epithelium interface. *Reproduction.* 160:887–903. doi: [10.1530/REP-20-0344](https://doi.org/10.1530/REP-20-0344)
- Stepniak, E., G. L. Radice, and V. Vasioukhin. 2009. Adhesive and signaling functions of cadherins and catenins in vertebrate development. *Cold Spring Harb. Perspect. Biol.* 1:a002949. doi: [10.1101/cshperspect.a002949](https://doi.org/10.1101/cshperspect.a002949)
- Takasuga, A. 2016. *PLAG1* and *NCAPG-LCORN* in livestock. *Anim. Sci. J.* 87:159–167. doi: [10.1111/asj.12417](https://doi.org/10.1111/asj.12417)
- Tang, Q., W. Wu, X. Xu, L. Huang, Q. Gao, H. Chen, H. Sun, Y. Xia, J. Sha, X. Wang, et al. 2013. miR-141 contributes to fetal growth restriction by regulating *PLAG1* expression. *PLoS One* 8:e58737. doi: [10.1371/journal.pone.0058737](https://doi.org/10.1371/journal.pone.0058737)

- Taye, M., W. Lee, S. Jeon, J. Yoon, T. Dessie, O. Hanotte, O. A. Mwai, S. Kemp, S. Cho, S. J. Oh, et al. 2017. Exploring evidence of positive selection signatures in cattle breeds selected for different traits. *Mamm. Genome* 28:528–541. doi: [10.1007/s00335-017-9715-6](https://doi.org/10.1007/s00335-017-9715-6)
- Telford, N. A., A. J. Watson, and G. A. Schultz. 1990. Transition from maternal to embryonic control in early mammalian development: a comparison of several species. *Mol. Reprod. Dev.* 26:90–100. doi: [10.1002/mrd.1080260113](https://doi.org/10.1002/mrd.1080260113)
- Tesfaye, D., N. Menjivar, and S. Gebremedhn. 2022. Current knowledge and the future potential of extracellular vesicles in mammalian reproduction. *Reprod. Fert. Develop.* 34:174–189. doi: [10.1071/rd21277](https://doi.org/10.1071/rd21277)
- Tkachenko, O. Y., S. Wolf, M. S. Lawson, A. Y. Ting, J. K. Rodrigues, F. Xu, C. V. Bishop, R. L. Stouffer, and J. Xu. 2021. Insulin-like growth factor 2 is produced by antral follicles and promotes pre-antral follicle development in macaques. *Biol. Reprod.* 104:602–610. doi: [10.1093/biolre/iaaa227](https://doi.org/10.1093/biolre/iaaa227)
- Utsunomiya, Y. T., A. S. do Carmo, R. Carvalheiro, H. H. R. Neves, M. C. Matos, L. B. Zavarez, A. M. P. O'Brien, J. Sölkner, J. C. McEwan, J. B. Cole, et al. 2013. Genome-wide association study for birth weight in Nellore cattle points to previously described orthologous genes affecting human and bovine height. *BMC Genet.* 14:52. doi: [10.1186/1471-2156-14-52](https://doi.org/10.1186/1471-2156-14-52)
- Utsunomiya, Y. T., M. Milanese, A. T. H. Utsunomiya, R. B. P. Torrecilha, E. S. Kim, M. S. Costa, T. S. Aguiar, S. Schroeder, A. S. do Carmo, R. Carvalheiro, et al. 2017. A *PLAG1* mutation contributed to stature recovery in modern cattle. *Sci. Rep.* 7:17140. doi: [10.1038/s41598-017-17127-1](https://doi.org/10.1038/s41598-017-17127-1)
- Valenta, T., G. Hausmann, and K. Basler. 2012. The many faces and functions of  $\beta$ -catenin. *EMBO J.* 31:2714–2736. doi: [10.1038/emboj.2012.150](https://doi.org/10.1038/emboj.2012.150)
- Van Dyck, F., J. Declercq, C. V. Braem, and W. J. M. Van de Ven. 2007. *PLAG1*, the prototype of the *PLAG* gene family: versatility in tumour development (review). *Int. J. Oncol.* 30:765–774. doi: [10.3892/ijo.30.4.765](https://doi.org/10.3892/ijo.30.4.765)
- Varrault, A., C. Gueydan, A. Delalbre, A. Bellmann, S. Houssami, C. Aknin, D. Severac, L. Chotard, M. Kahli, A. Le Digarcher, et al. 2006. *Zac1* regulates an imprinted gene network critically involved in the control of embryonic growth. *Dev. Cell* 11:711–722. doi: [10.1016/j.devcel.2006.09.003](https://doi.org/10.1016/j.devcel.2006.09.003)
- Visscher, P. M., and M. E. Goddard. 2011. Cattle gain stature. *Nat. Genet.* 43:397–398. doi: [10.1038/ng.819](https://doi.org/10.1038/ng.819)
- Voz, M. L., A. K. Åström, K. Kas, J. Mark, G. Stenman, and W. J. M. Van de Ven. 1998. The recurrent translocation t(5;8)(p13;q12) in pleomorphic adenomas results in upregulation of *PLAG1* gene expression under control of the *LIFR* promoter. *Oncogene* 16:1409–1416. doi: [10.1038/sj.onc.1201660](https://doi.org/10.1038/sj.onc.1201660)
- Voz, M. L., N. S. Agten, W. J. M. Van de Ven, and K. Kas. 2000. *PLAG1*, the main translocation target in pleomorphic adenoma of the salivary glands, is a positive regulator of *IGF-II*. *Cancer Res.* 60:106–113.
- Voz, M. L., J. Mathys, K. Hensen, H. Pendeville, I. Van Valckenborgh, C. Van Huffe, M. Chavez, B. Van Damme, B. De Moor, Y. Moreau, et al. 2004. Microarray screening for targets of the proto-oncogene *PLAG1*. *Oncogene* 23:179–191. doi: [10.1038/sj.onc.1207013](https://doi.org/10.1038/sj.onc.1207013)
- Wagner, G., and J. Zhang. 2011. The pleiotropic structure of the genotype–phenotype map: the evolvability of complex organisms. *Nat. Rev. Genet.* 12:204–213. doi: [10.1038/nrg2949](https://doi.org/10.1038/nrg2949)
- Wang, Y., W. Shang, X. Lei, S. Shen, H. Zhang, Z. Wang, L. Huang, Z. Yu, H. Ong, X. Yin, et al. 2013. Opposing functions of *PLAG1* in pleomorphic adenoma: a microarray analysis of *PLAG1* transgenic mice. *Biotechnol. Lett.* 35:1377–1385. doi: [10.1007/s10529-013-1213-7](https://doi.org/10.1007/s10529-013-1213-7)
- Wathes, D. C., G. E. Pollott, K. F. Johnson, H. Richardson, and J. S. Cooke. 2014. Heifer fertility and carry over consequences for life time production in dairy and beef cattle. *Animal.* 8:91–104. doi: [10.1017/S1751731114000755](https://doi.org/10.1017/S1751731114000755)
- Wei, Z., K. Wang, H. Wu, Z. Wang, C. Pan, H. Chen, and X. Lan. 2021D. Detection of 15-bp deletion mutation within *PLAG1* gene and its effects on growth traits in goats. *Animals.* 11:2064. doi: [10.3390/ani11072064](https://doi.org/10.3390/ani11072064)
- Willhelm, B. R., E. Ticiani, K. Campagnolo, G. B. de Oliveira, K. de Mattos, C. A. P. Bello, F. L. Ongaratto, P. Rodriguez-Villamil, L. Relly, J. P. M. Alves, et al. 2021. Promoter-specific expression of the imprinted *IGF2* gene in bovine oocytes and pre-implantation embryos. *Reprod. Dom. Anim.* 56:857–863. doi: [10.1111/rda.13925](https://doi.org/10.1111/rda.13925)
- Wong, J., A. R. Juma, S. C. Tran, J. G. Gasperoni, S. V. H. Grommen, and B. De Groef. 2020a. Deficiency of the transcription factor *PLAG1* results in aberrant coiling and morphology of the epididymis. *Asian J. Androl.* 22:342–347. doi: [10.4103/aja.aja\\_87\\_19](https://doi.org/10.4103/aja.aja_87_19)
- Wong, J., A. Damdimopoulos, P. Damdimopoulou, J. G. Gasperoni, S. C. Tran, S. V. H. Grommen, B. De Groef, and S. Dworkin. 2020b. Transcriptome analysis of the epididymis from *Plag1* deficient mice suggests dysregulation of sperm maturation and extracellular matrix genes. *Dev. Dyn* 249:1500–1513. doi: [10.1002/dvdy.254](https://doi.org/10.1002/dvdy.254)
- Wu, H., Y. Pan, Q. Zhang, Y. Cao, J. Li, H. Chen, Y. Cai, X. Sun, and X. Lan. 2019. Insertion/deletion (InDel) variations in sheep *PLAG1* gene locating in growth-related major QTL are associated with adult body weight and morphometric traits. *Small Ruminant Res.* 178:63–69. doi: [10.1016/j.smallrumres.2019.08.003](https://doi.org/10.1016/j.smallrumres.2019.08.003)
- Xu, W., H. He, L. Zheng, J. W. Xu, C. Z. Lei, G. M. Zhang, R. H. Dang, H. Niu, X. L. Qi, H. Chen, et al. 2018. Detection of 19-bp deletion within *PLAG1* gene and its effect on growth traits in cattle. *Gene* 675:144–149. doi: [10.1016/j.gene.2018.06.041](https://doi.org/10.1016/j.gene.2018.06.041)
- Xu, H., H. Li, Z. Wang, A. Abudureyimu, J. Yang, X. Cao, X. Lan, R. Zang, and Y. Cai. 2020. A deletion downstream of the *CHCHD7* gene is associated with growth traits in sheep. *Animals (Basel).* 10:1472. doi: [10.3390/ani10091472](https://doi.org/10.3390/ani10091472)
- Zatkova, A., J. M. Rouillard, W. Hartmann, B. J. Lamb, R. Kuick, M. Eckart, D. von Schweinitz, A. Koch, C. Fonatsch, T. Pietsch, et al. 2004. Amplification and overexpression of the *IGF2* regulator *PLAG1* in hepatoblastoma. *Genes Chromosomes Cancer* 39:126–137. doi: [10.1002/gcc.10307](https://doi.org/10.1002/gcc.10307)
- Zhang, R., J. Miao, Y. Song, W. Zhang, L. Xu, Y. Chen, L. Zhang, H. Gao, B. Zhu, J. Li, et al. 2019. Genome-wide association study identifies the *PLAG1-OXR1* region on BTA14 for carcass meat yield in cattle. *Physiol. Genom.* 51:137–144. doi: [10.1152/physiolgenomics.00112.2018](https://doi.org/10.1152/physiolgenomics.00112.2018)
- Zhao, F., S. McParland, F. Kearney, L. Du, and D. P. Berry. 2015. Detection of selection signatures in dairy and beef cattle using high-density genomic information. *Genet. Sel. Evol.* 47:49. doi: [10.1186/s12711-015-0127-3](https://doi.org/10.1186/s12711-015-0127-3)
- Zhong, J. L., J. W. Xu, J. Wang, Y. F. Wen, H. Niu, L. Zheng, H. He, K. Peng, P. Hea, S. Y. Shi, et al. 2019. A novel SNP of *PLAG1* gene and its association with growth traits in Chinese cattle. *Gene* 689:166–171. doi: [10.1016/j.gene.2018.12.018](https://doi.org/10.1016/j.gene.2018.12.018)
- Zhou, Z., B. Huang, Z. Lai, S. Li, F. Wu, K. Qu, Y. Jia, J. Hou, J. Liu, C. Lei, et al. 2019. The distribution characteristics of a 19-bp indel of the *PLAG1* gene in Chinese cattle. *Animals (Basel).* 9:1082. doi: [10.3390/ani9121082](https://doi.org/10.3390/ani9121082)
- Zhou, C., M. Lv, P. Wang, C. Guo, Z. Ni, H. Bao, Y. Tang, H. Cai, J. Lu, W. Deng, et al. 2021. Sequential activation of uterine epithelial *IGF1R* by stromal *IGF1* and embryonic *IGF2* directs normal uterine preparation for embryo implantation. *J. Mol. Cell. Biol.* 13:646–661. doi: [10.1093/jmcb/mjab034](https://doi.org/10.1093/jmcb/mjab034)