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Review article

Polymorphisms and genes associated with puberty in heifers

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ABSTRACT

Puberty onset is a multifactorial process influenced by genetic determinants and environmental conditions, especially nutritional status. Genes, genetic variations, and regulatory networks compose the molecular basis of achieving puberty. In this article, we reviewed the discovery of multiple polymorphisms and genes associated with heifer puberty phenotypes and discuss the opportunities to use this evolving knowledge of genetic determinants for breeding early pubertal *Bos indicus*–influenced cattle. The discovery of polymorphisms and genes was mainly achieved through candidate gene studies, quantitative trait loci analyses, genome-wide association studies, and recently, global gene expression studies (transcriptome). These studies are recapitulated and summarized in the current review.

1. Introduction

Puberty in cattle is both a developmental process and a classic quantitative trait. It is now evident that the occurrence of puberty in mammals, including heifers, is mediated by a regulatory gene network composed of multiple functional modules [1–4]. In other words, puberty is influenced by many interacting genes. For evidence, mutations in genes such as *GPR54* [5,6], *GNRHR* [7], *TAC3*, *TACR3* [8], and *KiSS1* [9] have been linked to failure of pubertal development in mammals. Genome-wide association studies (GWAS) in cattle and humans have identified multiple genes associated with female puberty [10–12]. Processes or phenotypes controlled by multiple genes are by definition quantitative traits [13]. Complex quantitative traits are heritable and can be used in selection strategies in breeding programs.

Breeding cattle for earlier puberty onset is especially desirable in *Bos indicus* and *Bos indicus*–influenced breeds. *Bos indicus* cattle and their crosses are generally older at puberty when compared with *Bos taurus* [14]. Breed differences were observed in heifers, with *Bos indicus* females reported to achieve puberty at an older age than *Bos taurus* on average [15–18]. Late puberty is a disadvantage in terms of reproductive efficiency and therefore efforts to breed cattle for early puberty are already part of several genetic improvement programs [19–21]. However, most phenotypes related to heifer puberty (e.g., age at first ovulation) can be expensive and difficult to measure on farm. Heifer puberty phenotypes are likely to benefit from genomic technologies seen as an avenue to improve selection accuracy and genetic gain for phenotypes that are a challenge to measure and are sex limited [22,23]. Furthermore, knowledge of specific genes, mutations, gene networks,

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and pathways can be used to enhance genomic selection [24–26]. In this article, we reviewed the discovery of multiple polymorphisms and genes that were associated with female puberty onset in cattle and discuss the opportunities to use the emerging knowledge of genetic determinants for breeding early pubertal *Bos indicus*–influenced cattle.

1.1. Puberty onset and the regulation of GnRH release

The central control of reproduction in mammals takes place in the hypothalamus, which is the site of expression and action for a number of molecular factors controlling puberty onset. One "maestro" is considered the trigger or the gate keeper for puberty onset: GnRH. The hypothalamic release of pulsatile GnRH is paramount for mammalian puberty because it triggers downstream release of LH and FSH, the hormones necessary for gonadal steroidogenesis and gametogenesis. Nonetheless, upstream from GnRH release, a tightly regulated gene network forms an "orchestra" of interacting signals and pathways: all relevant to the pubertal process and timing. The current hypothesis to explain puberty discusses the roles of multiple puberty-activating and puberty-delaying genes upstream to GnRH release [27]. The cross-talk between permissive nutritional signals (e.g., leptin) and inhibitory gonadal signals (e.g., estradiol) also occur upstream from GnRH [28]. The concept is that, the early stages of puberty are mediated by transcriptional and post-transcriptional repression genes that suppress puberty-activating genes, inhibiting GnRH release and therefore the pubertal process. This physiological response is typically described as the biphasic endocrine response to estradiol [29]. From these concepts, we suggest that the level of expression of puberty-delaying genes is initially high, whereas the expression of puberty-activating genes is minimal (prepuberty). This trend would be reversed with increased expression of puberty-activating genes on the onset of puberty.

Known players in the "orchestra" upstream from GnRH release are insulin-like growth factor 1 (*IGF1*), leptin (*LEP*), kisspeptin (*KiSS1*), neuropeptide Y (*NPY*), adiponectin (*ADIPOQ*), proopiomelanocortin (*POMC*), and their associated trans-synaptic pathways. Increasing serum leptin, *LEP* expression, serum IGF1, and body weight were reported for peripubertal *Bos indicus*–influenced heifers before first ovulation [30]. Exogenous leptin administered to heifers is capable of rising LH concentrations [31,32]. Downstream of the leptin signal, *KiSS1* neurons communicate with *POMC* and *NPY* pathways that regulate GnRH release [33–37]. The observation that *POMC* expression increases in response to elevated nutrition supports the theory that *POMC* neurons mediate the effect of leptin on puberty [38]. Another molecular link between energy metabolism and puberty is adiponectin, which decreases *KiSS1* transcription and suppresses GnRH release [39,40]. The injection of adiponectin into the hypothalamus increases phosphorylation levels of insulin receptor substrates, such as *IRS-1* or *IRS-2* [41]. These observations demonstrate the cross-talk between adiponectin, leptin, and insulin pathways in hypothalamus, which link nutritional status with puberty [38,41]. The link between energy homeostasis and puberty were explored in candidate gene studies discussed herein.

1.2. Candidate genes associated to heifer puberty

Candidate gene studies use a targeted approach: genes are selected for association analyses based on their function, which are not genome wide. A few candidate gene studies have tested the association of polymorphisms in biologically relevant genes with puberty phenotypes. For example, genes of the IGF1 pathway were associated to heifer puberty phenotypes in two separate studies [42,43]. In a third study, the gene *PAPP-A2*, which plays a role in IGF1 metabolism was associated to fertility phenotypes in Holstein cattle [44].

Two larger candidate gene approaches were performed recently. Genotypes for 434 candidate single nucleotide polymorphisms (SNPs) were tested, yielding 40 SNPs associated with fertility traits in Holstein heifers [45]. Associations for heifer conception rate were reported for the genes: *DEPDC7*, *LDB3*, *MS4A8B*, *PARM1*, and *TDRKH* [45]. In another study, 57 genes involved in lipid metabolism were targeted for association analyses in Nelore cattle measured for sexual precocity [46]. Only two of 57 genes were significant: *FABP4* and *PPP3CA*. Candidate gene studies are biased because they only target genes already known for their biological role (i.e., know to play a role in puberty onset or nutritional signalling). However, the fact that GnRH is crucial for puberty biologically does not imply that this (or any other known candidate gene) carries a significant polymorphism. In contrast, genome-wide studies involving "omic" strategies (i.e., DNA–RNA–protein) have the potential to point to new candidate genes as follows.

1.3. Genomic regions and polymorphisms associated with puberty in heifers

Association analyses have identified many polymorphisms associated with puberty phenotypes in heifers. Older studies used microsatellites to detect quantitative trait loci (QTL), whereas more modern studies used SNPs to identify association regions. Associated polymorphisms flag genomic regions harboring QTL, which can be traced for identification of genes linked to puberty phenotypes. A great number of associations discovered in cattle are published in databases, such as the AnimalQTLdb (Hu et al., 2007; http://www.animalgenome.org/cgi-bin/QTLdb/index). Such databases and literature were queried to compile a list of genomic regions associated with heifer puberty phenotypes (Table 1).

Puberty needs to be defined and measured as a phenotype so that association analyses can be performed. Nine heifer puberty phenotypes were used in these studies: (1) age at first calving, (2) age at first estrus, (3) age at first service, (4) age at first CL, (5) first service conception, (6) heifer pregnancy, (7) interval from the first to last service heifer, (8) nonreturn rate heifer, and (9) number of inseminations per conception per heifer. The first four phenotypes can be considered more direct measurements of