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Review

Association between somatotropic axis gene polymorphisms and reproductive efficiency of bovine females: a review

Associação entre polimorfismos de genes do eixo somatotrópico e eficiência reprodutiva de fêmeas bovinas: revisão de literatura

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Abstract
Reproductive characteristics directly reflect on productive performance, as they determine the number of calves born annually and the interval between generations, thereby affecting the selection intensity. This allows for the determination of the most important economic variables that directly affect the production system. The present study is a literature review of somatotropic axis gene polymorphisms that are associated with reproductive functions in heifers and cows (*Bos taurus taurus* and *Bos taurus indicus*). The following characteristics were analyzed from the various studies reviewed: number of services per pregnancy (Nº services/pregnancy), age at first calving (AFC), calving interval (CI), and period of service calving conception interval (CCI). The research was conducted during the period from 2011 to 2021, and associations were found among all indicators of reproductive efficiency evaluated in heifers and cows, with 27 single nucleotide polymorphisms (SNPs): 18 in *GHR*, 5 in *IGF-I*, and 4 in *STAT5A*. This study revealed the relationships between SNPs and the reproductive efficiency indicators and demonstrated that molecular genetic techniques enhance the animal selection process, resulting in more profitable systems that are sustainable in the long term.
Keywords: Molecular genetics; *IGF-I*; Animal reproduction; SNPs; *STAT5A*.

Resumo
Características reprodutivas refletem diretamente no desempenho produtivo visto que são capazes de determinar o número de bezerros nascidos anualmente, além de afetar o intervalo entre gerações e, consequentemente, a intensidade de seleção, fazendo com o que tais atributos sejam apontados como variáveis econômicas das mais importantes que afetam diretamente o sistema de produção. O presente estudo propõe realizar uma revisão de literatura de polimorfismos de genes do eixo somatotrópico associados a funções reprodutivas em novilhas e vacas (*Bos taurus taurus* e *Bos taurus indicus*), indicadas pelos índices: número de serviços por gestação (Nº serviços/gestação), idade ao primeiro parto (IPP), intervalo de partos (IP) e período de serviço, como também denominado de intervalo parto-concepção (IPC). As pesquisas encontradas durante o período de 2011 a 2021 demonstraram associações entre todos os indicadores de eficiência reprodutiva analisados de novilhas e vacas com 27 polimorfismos de nucleotídeo único (SNPs), sendo 18 em *GHR*, 5 em *IGF-I* e 4 em *STAT5A*. Dessa forma, este estudo mostrou relação entre os SNPs e os indicadores de eficiência reprodutiva, demonstrando que técnicas de genética molecular potencializam o processo de seleção dos animais, resultando em sistemas mais lucrativos e que se sustentam a longo prazo.
Palavras-chave: Genética molecular; *IGF-I*; Reprodução animal; SNPs; *STAT5A*.

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Introduction

The reproductive characteristics of heifers affect productive performance, since they can determine the number of calves born annually(1). They are also involved in defining the generation interval, and consequently, the selection intensity(2), thereby indicating the economic attributes that substantially affect the production system. According to Grossi et al.(3), animals that prolong the period prior to reproduction and do not procreate regularly, prove to be unviable for production systems, whether beef or dairy; therefore, animals must be selected that have the essential reproductive characteristics to comprise the herds.

Normally, reproductive traits have low heritability(4) and are highly influenced by the environment, which complicates the association of phenotype with reproductive attributes, thereby requiring a more direct analysis of their relationship with genetic aspects. Recently, genotype-based selection(5) has contributed to reducing some of the limitations of traditional selection methods(6) and has actively contributed to the progress of animal breeding(7). Molecular markers are tools that allow the identification of genetic variations in DNA, since most of the characteristics of economic interest are quantitative and controlled by several genes whose independent effects contribute to the final phenotype(5) along with the environment and genotype-environment interactions.

The study of polymorphisms and their association with productivity indices, such as reproductive parameters, will help genetic improvement programs that contribute to the early selection of animals based on characteristics directly linked to the economic success of the activity. Thus, the present study is a literature review of somatotropic axis gene polymorphisms associated with reproductive functions in heifers and cows (*Bos taurus taurus* and *Bos taurus indicus*) indicated by the number of services per pregnancy (Nº services/pregnancy), age at first calving (AFC), calving interval (CI), and period of service determined by the calving conception interval (CCI) or number of days open, depending on the reference.

Genetic improvement of cattle

Classical breeding programs use phenotypic information in the form of expected progeny difference (EPD), which is half of the predicted genetic value and represents the expected deviation from the mean of the offspring of a given individual for a certain trait in relation to the genetic basis of the evaluated population. More accurate EPDs correspond to greater genetic progress, as this information is used for selection; therefore, greater gains are achieved as the predicted value approaches the real (true) genetic merit. In addition, highly accurate EPDs that are obtained early allow for more rapid genetic advances of a herd/population as a result of the more intense use of young animals in reproduction(8). Obtaining high accuracy using this traditional methodology for genetic selection takes time, as the animals need to present offspring for evaluation, especially with regard to reproductive traits.

Since the early 2000s, molecular genetic technologies, which allow access and manipulation of the genome, have rapidly evolved and increased in usage, and several approaches have emerged for genetic improvements using these technologies, including those with the objective of increasing the accuracy of genetic evaluations of beef cattle and enabling a more timely use of young animals. The results from dairy and beef cattle breeding programs conducted in North America and Europe have shown that if genomic data are used in conjunction with phenotypic and genealogical data, the benefits can be significant. Therefore, genomics has brought a vast group of new concepts to breeders/selectors, such as single nucleotide polymorphism (SNP) markers(8).

The greatest challenge is determining how knowledge of the genome can be applied viably and effectively to genetically improve beef and dairy cattle(8). The Zebu Genetic Improvement Program summary, conducted by the Brazilian Association of Zebu Breeders (ABCZ), provides genomic information for the selection of all characteristics presented in the summary through information obtained from several SNPs for each characteristic using a complex matrix and mathematical models(9).

The greatest limitation today no longer relates to understanding the sequence of genes(10) or presenting domestic animal data in a practical way(11), but rather identifying the genes that have the greatest impact on the control of characteristics of zootechnical interest, such as those that confer resistance to diseases (endo-and ectoparasites) and heat, and those that relate to better feed conversion and greater reproductive efficiency(10). With the identification and association of these genes or SNPs, selection can become more efficient and greater responses can be achieved in practice. Thus, it appears that the main advantage of genomic selection usage is the increased accuracy of genetic evaluations of animals(12) in cases where phenotypic expression is greatly influenced by uncontrolled sources of variation, such as that of reproductive traits, individuals who are not phenotyped, and/or those with no or few evaluated offspring (applying AFC)(9).

Single nucleotide polymorphism (SNP) markers

Recent advances in high-throughput DNA sequencing, software, and bioinformatics have facilitated the identification of SNP markers from amplified segments of genomic DNA(13), which aid in the identification of favorable alleles for selection in different fields of animal production. Sharifiyazdi, Mirzaei, and Ghanaatian(14) investigated point mutations (A/G: position -278) in the 5' region of the gene responsible for the expression of the follicle stimulating hormone receptor (*FSHR*) of Iranian dairy cattle, and found an association between this mutation and reproductive parameters. Cows that did not present the G allele (AA) showed more desirable fertility, with lower average Nº services/pregnancy (1.98±0.77 vs 2.20±0.85) and number of days open (118.3±42 vs 118.7±49.3).

For beef cattle, Meyer et al.(15) associated polymorphisms present in the bovine prolactin (*Prl*) gene with other phenotypic characteristics, and found six haplotypes for the bovine *Prl* gene, with emphasis on the CAG haplotype. Animals had higher birth rates (96, 91, 90, 81, 86, and 81%) and higher pregnancy rates (43.4, 42.7, 42.8, 42.8, 40.8, and 37.7%, $p<0.05$) when they presented this haplotype.

Another study identified two polymorphisms in the *PPP3CA* gene (protein phosphatase 3 - catalytic subunit, alpha isoenzyme) and 13 in the *FABPA* gene (fatty acid binding protein 4), whereby two SNPs located in the *FABP4* gene (rs109014985 and rs134173517) exerted a significant effect on the probability of early pregnancy at 16 months (P16) in Nelore heifers ($P<0.05$)(16), demonstrating the contribution of this gene, and consequently, of lipid metabolism, to reproduction. The aspects described above demonstrate the increasing use of the association of SNPs with characteristics of zootechnical interest, particularly those in relation to reproduction.

Relationships among the somatotropic axis and SNPs of the GHR, IGF-I, and STAT5A genes and their effect on reproductive physiology

Growth regulation is guided by the growth hormone-insulin-like growth factor type I (*GH–IGF-I*) axis, also called the somatotropic axis (Figure 1).

The hypothalamus produces and secretes growth hormone-releasing hormone (*GHRH*), which acts on the anterior pituitary gland to stimulate somatotropic production of *GH* (somatotropin). This stimulates target organs and tissues, especially the liver, to produce and release *IGF-I* or somatomedin, which mediates the retroactivity of the *GH–IGF-I* system(17). In addition, *GH* promotes *IGF-I* gene expression through the activation of intracellular Janus kinase and signal transducer and transcriptional activator (*STAT*) families, such as *STAT5A*(18). This pathway is essential for cell growth, differentiation, and development of various tissues, particularly the modulation and amplification of gonadotropin, follicle stimulating hormone (FSH), and luteinizing hormone (LH) activities during follicular growth in the ovary(19).

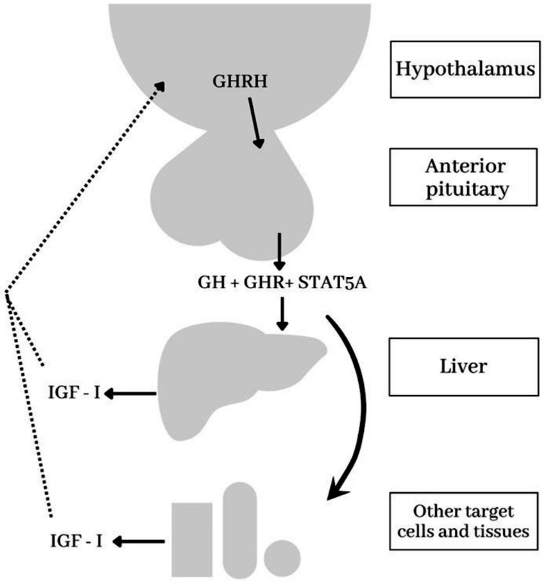

Figure 1. Anatomophysiological model of the somatotropic axis.

In cattle, *GH* and *IGF-I* receptor genes are expressed in several tissues, and their differential regulation occurs in the liver and tissues of the reproductive system(20). In the postpartum period of high-production dairy cows, negative energy balance (NEBAL) is associated with the loss of body condition and delay in the return of cyclic luteal ovarian activities, resulting in ovulation failure and reduced conception rates after delivery (21). The link between NEBAL and reproductive failure during this period has been justified by the uncoupling of the secretion of *GH* and *IGF-I* by the liver due to the reduction in the release of insulin(19).

The genes that encode *GH* and *IGF-I* form the somatotropic axis, along with the related receptors and several signaling proteins present in cells, such as signal transducer and activator 5A (*STAT5A*); therefore, the somatotropic axis is the main regulator of both reproductive physiology and mammalian metabolism(17). Polymorphism is directly and indirectly related to the phenotype in these genes, mainly in relation to milk composition and synthesis (22), meat and carcass production properties(23) and reproductive activities(24).

Hax et al.(25) found no association between the polymorphisms AluI (Gene *GHR*) and SnaBI (Gene *IGF-I*) present in genes of the somatotropic axis and reproductive performance in Holstein dairy cows; however, they observed that the BstEII (+) SNP (Gene *STAT5A*) was associated with a shorter calving first heat interval. They suggested that this gene can be used as a molecular marker to enhance the reproductive performance of Holstein herds, and that future research could extend the study to different categories, such as heifers, beef cows, and different subspecies.

Relationships among SNPs in the GHR, IGF-I, and STAT5A genes and reproductive efficiency indicators

The bibliographic research mainly obtained information from the National Center for Biotechnology Information (NCBI), which was searched using the PubMed platform and the names of genes and reproductive parameters as keywords over a ten years period, 2011 – 2021. The selected data were race, heifer or cow, genotype, polymorphic allele, genotypic frequency, allele frequency, location of the polymorphism, Nº services/pregnancy, AFC, CI, and CCI. After selection, the data were organized in a Microsoft Excel spreadsheet for further comparative analysis of the effects of *GHR, IGF-I*, and *STAT5A* markers on reproduction characteristics.

In 2011, 2012, 2014, 2018, 2019, and 2020, one article was published per year; two articles per year were published in 2013 and 2017; no reports were found in 2015, 2016, and 2021; and the most recent publication occurred in 2020 (Figure 2). The high cost of the technology and methods used to obtain the data may limit the performance of this type of research, which explains the lack of available information in the literature.

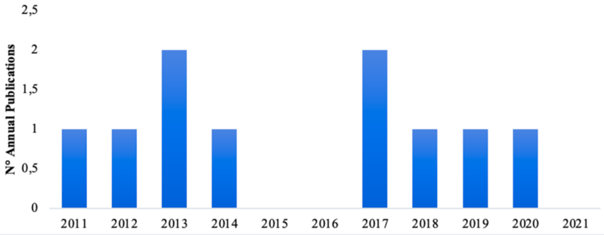

Figure 2. Evolution of the last 10 years (2011-2021) of updated scientific publications, seeking association of polymorphisms present in the *GHR, IGF-I* and *STAT5A* genes with the reproductive performance of cows and heifers using the PubMed platform.

The research found during these 10 years showed and correlated the SNPs with the reproductive characteristics in heifers and cows, with a total of 27 SNPs: 18 in *GHR*, 5 in *IGF-I*, and 4 in *STAT5A*. Tables 1, 2, and 3 show the information on the location of the SNPs, as well as the indices and/or characteristics evaluated, such as the Nº services/pregnancy, CI, CCI, and AFC. All studies were conducted on taurine species and aimed at heifers and cows in the lactation period. From the studies analyzed for the *GHR* gene, all SNPs were tested with cows, whereas for the *IGF-I* gene four SNPs were tested with cows and one with heifers, and for the *STAT5A* gene, three SNPs were tested with cows and one with heifers.

Table 1. *GHR* SNPs associated with increase, decrease or maintenance of reproductive characteristics such as calving interval (CI), calving conception interval (CCI), age at first calving (AFC) and number of services per pregnancy (Nº services/pregnancy)

SNP	Polymorphic Region	Subspecies	Heifer / Cow	Evaluated characteristic	Effect of association of the SNP with the evaluated characteristic	Reference
GHR/AluI	Regulatory region	Bos taurus taurus	Cow	Nº services/pregnancy; CI; CCI	Maintained	Hax et al.[25]
GHR/AluI	Regulatory region	*Bos taurus taurus*	Cow	Nº services/pregnancy	Decreased	Schneider et al.[24]
GHR_rs41 639262	Unspecific	*Bos taurus taurus*	Cow	CCI	Decreased	Leyva-Corona et al.[26]
GHR1.1	Non-coding region 5′	*Bos taurus taurus*	Cow	CI	Decreased	Waters et al.[27]
GHR2.6	Non-coding region 5′	*Bos taurus taurus*	Cow	CI	Decreased	Waters et al.[27]
GHR4.1	Non-coding region 5′	*Bos taurus taurus*	Cow	CI	Decreased	Waters et al.[27]
GHR4.2	Non-coding region 5′	*Bos taurus taurus*	Cow	CI	Decreased	Waters et al.[27]
GHR6.1	Non-coding region 5′	*Bos taurus taurus*	Cow	CI	Decreased	Waters et al.[27]
GHR9.1	Non-coding region 5′	*Bos taurus taurus*	Cow	CI	Decreased	Waters et al.[27]
AF126288: g.149	1st exon promoter	*Bos taurus taurus*	Cow	CI	Decreased	Waters et al.[27]
GHR19.1	Intron 2-3	*Bos taurus taurus*	Cow	CI	Decreased	Waters et al.[27]
F279Y	Exon 8	*Bos taurus taurus*	Cow	CI	Decreased	Waters et al.[27]
N528T	Exon 10	*Bos taurus taurus*	Cow	CI	Decreased	Waters et al.[27]
A536T	Exon 10	*Bos taurus taurus*	Cow	CI	Decreased	Waters et al.[27]
H545	Exon 10	*Bos taurus taurus*	Cow	CI	Decreased	Waters et al.[27]
S555G	Exon 10	*Bos taurus taurus*	Cow	CI	Decreased	Waters et al.[27]
g.914T>A	Exon 8	*Bos taurus taurus*	Cow	CI	Decreased	Fedota et al.[28]
g.257A>G	Exon 10 promoter	*Bos taurus taurus*	Cow	CI	Decreased	Fedota et al.[28]

Single nucleotide polymorphisms (SNPs); calving interval (CI); calving conception interval (CCI); Age at first calving (AFC).

Table 2. *IGF-I* SNPs associated with increase, decrease or maintenance of reproductive characteristics such as calving interval (CI), calving conception interval (CCI), age at first calving (AFC) and number of services per pregnancy (Nº services/pregnancy)

SNP	Polymorphic Region	Subspecies	Heifer/ Cow	Evaluated characteristic	Effect of the association of the SNP with the trait evaluated	Reference
IGF-I/SnaBI	Exon 1	*Bos taurus taurus*	Cow	Nº services/ pregnancy; CI; CCI	Maintained	Hax et al.(25)
IGF-I/SnaBI	Promoter Region	*Bos taurus taurus*	Cow	Nº services/ pregnancy; CCI	Decreased	Silveira et al. (29)
Transição T→ C	Exon 4-5	*Bos taurus taurus*	Heifer	Nº services/ pregnancy; AFC; CI	Maintained	Abdolmohammadi et al. (30)
IGF-I_rs109763947	Unspecific	*Bos taurus taurus*	Cow	Nº services/ pregnancy	Decreased	Leyva-Corona et al. (26)
IGF-I/SnaBI	Promoter Region	*Bos taurus taurus*	Cow	CCI	Maintained	Nicolini et al. (31)

Single nucleotide polymorphisms (SNPs); calving interval (CI); calving conception interval (CCI); Age at first calving (AFC).

Table 3. *STAT5A* SNPs associated with increase, decrease or maintenance of reproductive characteristics such as calving interval (CI), calving conception interval (CCI), age at first calving (AFC) and number of services per pregnancy (Nº services/pregnancy)

SNP	Polymorphic Region	Subspecies	Heifer / Cow	Evaluated characteristic	Effect of the association of the SNP with the trait evaluated	Reference
STAT5A/ BstEII	Exon 8	*Bos taurus taurus*	Cow	Nº services/pregnancy; CI; CCI	Maintained	Hax et al. (25)
STAT5A/ BstEII	Exon 8	*Bos taurus taurus*	Cow	Nº services/pregnancy; CCI	Decreased	Silveira et al. (29)
SNP12195	Exon 8	*Bos taurus taurus*	Heifer	Nº services/pregnancy; AFC; CCI	Maintained	Oikonomou et al. (32)
SNP12195	Exon 8	*Bos taurus taurus*	Cow	Nº services/pregnancy; CCI	Maintained	Michel-Regalado et al. (33)

Single nucleotide polymorphisms (SNPs); calving conception interval (CCI); Age at first calving (AFC).

GH promotes physiological processes involved in milk production and postnatal growth in cattle(34). Several studies have shown that the *IGF-I* gene plays an important role in lactation, by indicating the energy balance at the beginning of lactation and maintaining ovarian function(35). Therefore, Pryce et al.(36) suggested that if this gene is considered for genomic selection, high concentrations of the *IGF-I* hormone will promote an improvement in reproductive indices and increase the performance of animals in bovine genetic improvement programs. Aggrey et al.(37) identified *GHR*/AluI (switch from A to T, located at position 1182) as a polymorphism. The effects of the *GHR*/AluI SNP on the reproductive function of 94 Holstein cows were also evaluated by studying two reproductive indicators, the N° services/ pregnancy and CCI(23). Schneider et al.(24) observed a linear reduction in CCI and a reduction in the number of AI/conceptions.

Leyva-Corona et al.(26) studied the effect of *GHR* gene SNPs (rs41639262) and the *IGF-I* gene marker (rs109763947) on traits that indicate reproductive efficiency, using 659 Holstein cows raised in an artificial hot-humid climate. The reproductive indicator evaluated in this study was the CCI, which is classified as a molecular marker suggested for a selection program to improve the fertility and production of dairy cattle, since the CCI was significantly reduced in this study. Abdolmohammadi et al.(30) evaluated the influence of the C allele (T/C transition) in the middle and terminal regions of the IGF-I gene on the reproductive performance of Iranian Holstein females. All indices evaluated showed good zootechnical performance related to the SNP; however, the difference was not significant ($p > 0.05$); therefore, it was classified as a nonfunctional variant. The CI values did not change in the presence of the polymorphism.

The collected bibliographic research showed a numerical relationship between the effect of SNPs on the indicators of reproductive efficiency CCI, AFC, CI, and Nº services/pregnancy of cows and heifers. This can be observed in the comparisons in Tables 4, 5, and 6. CCI is interlinked with several factors, such as the voluntary waiting period (defined by each farm), heat detection and conception rate, artificial insemination (AI) techniques, birth season, breed, herd size, herd production, and lactation number of cows(38). As shown in Table 4, this period has been commonly used and has been successful for reproductive management, as cows with higher CCI have more health problems, greater chances of beinged, and increased risks of weight loss until the end of lactation (the milk production of these cows drops at a faster rate than the dry matter intake), causing increased feeding, which raises the cost of production(38).

Table 4. Relationship between SNPs and the increase, decrease or maintenance of the calving-conception interval (CCI) reproductive efficiency indicator, for cows and heifers

Author/Year	SNP	CCI/days		
		AI	ET	Effect of the association of the SNP with the trait evaluated
Hax et al.(25)	GHR/AluI	111	-	Maintained
Hax et al.(25)	GHR/AluI	105	-	Maintained
Hax et al.(25)	GHR/AluI	112	-	Maintained
Hax et al.(25)	GHR/AluI	132	232	Maintained
Hax et al.(25)	GHR/AluI	118	231	Maintained
Hax et al.(25)	GHR/AluI	133	235	Maintained
Leyva-Corona et al.(26)	GHR_rs41639262	133	-	Decreased
Leyva-Corona et al.(26)	GHR_rs41639262	133	-	Decreased
Hax et al.(25)	IGF-I/SnaBI	109	-	Maintained
Hax et al.(25)	IGF-I/SnaBI	109	-	Maintained
Hax et al.(25)	IGF-I/SnaBI	112	-	Maintained
Hax et al.(25)	IGF-I/SnaBI	131	235	Maintained
Hax et al.(25)	IGF-I/SnaBI	151	221	Maintained
Hax et al.(25)	IGF-I/SnaBI	130	239	Maintained
Silveira et al.	IGF-I/SnaBI	78	-	Decreased
Silveira et al.(29)	IGF-I/SnaBI	97	-	Decreased
Silveira et al.(29)	IGF-I/SnaBI	109	-	Decreased
Nicolini et al.(31)	IGF-I/SnaBI	91	-	Maintained
Nicolini et al. (31)	IGF-I/SnaBI	92	-	Maintained
Nicolini et al. (31)	IGF-I/SnaBI	87	-	Maintained
Hax et al.(25)	STAT5A/BstEII	113	-	Decreased
Hax et al.(25)	STAT5A/BstEII	111	-	Decreased
Hax et al.(25)	STAT5A/BstEII	108	-	Decreased
Hax et al.(25)	STAT5A/BstEII	138	239	Decreased
Hax et al.(25)	STAT5A/BstEII	141	238	Decreased
Hax et al.(25)	STAT5A/BstEII	122	228	Decreased
Silveira et al.(29)	STAT5A/BstEII	94	-	Decreased
Silveira et al.(29)	STAT5A/BstEII	102	-	Decreased
Silveira et al.(29)	STAT5A/BstEII	101	-	Decreased
Michel-Regalado et al.(33)	SNP12195	67	-	Maintained
Michel-Regalado et al.(33)	SNP12195	69	-	Maintained
Michel-Regalado et al. (33)	SNP12195	74	-	Maintained

Single nucleotide polymorphisms (SNPs); Artificial insemination (AI); Embryonic transfer (ET); Missing data (-).

In contrast, Shirasuna et al.(39) and Hax et al.(25) found lower CCI in cows with the G allele for the polymorphism in the *STAT5A* gene. The effect of this allele may be due to the role of the gene in the *GH* signaling pathway, as *STAT* proteins are activated to regulate gene transcription, which increases the level of *IGF-I*. This hormone increases estradiol production in the follicle, triggering early ovulation(40). Homer et al.(41) found that cows with the G allele for the *STAT5A* gene presented higher estrus expression, which may be due to the greater increase in estradiol production in the follicle.

AFC is considered a selection method as it is directly related to age at puberty. Earlier puberty allows females to become productive sooner and increase the number of pregnancies during their lifetimes, which results in greater amounts of milk produced and number of calves available for replacement or sale, thereby increasing the cash flow of the farm(42).

The T/C transition located in the promoter region of the *IGF-I* gene may indicate the serum concentration of *IGF-I* in Holstein cows from Iran. The variant has been reported in this population of dairy cattle from Iran as not functional, and it is likely that the low association of the SNP (given by the significance value) with these characteristics relates to a linkage disequilibrium with other variants at the IGF-I or quantitative trait loci (QTL) that are reported in this location(30) (Table 5).

Table 5. Relationship between SNPs and the age at first calving (AFC) reproductive efficiency indicator for cows and heifers

Author/Year	SNP	AFC/days
Abdolmohammadi; Zamani (30)	Transition T/C	895,4
Abdolmohammadi; Zamani (30)	Transition T/C	889,3
Abdolmohammadi; Zamani (30)	Transition T/C	895,4
Abdolmohammadi; Zamani (30)	Transition T/C	889,3
Oikonomou et al.(32)	SNP12195	820
Oikonomou et al.(32)	SNP12195	-
Oikonomou et al.(32)	SNP12195	820

Single nucleotide polymorphisms (SNPs); Age at first calving (AFC); Missing data (-).

Waters et al.(27) genotyped 13 SNPs and correlated them with milk production, fat production, protein production/fat percentage, protein percentage, somatic cell score, survival, growth characteristics, and calving interval (Table 6).

The CI can be defined as the period between two consecutive calvings, and it measures both individual and herd reproductive efficiency. To obtain the maximum milk production/day, calving should be maintained at intervals of 12 to 14 months. Longer CIs can cause the next parturition to be delayed, thus increasing the time to the next progeny and the next lactation and decreasing production; hence, it is important to maintain focus on the zootechnical indicators(42). Fedota et al.(28) analyzed the reproductive characteristics of *A. angus* cows and showed that the CI in cows with the CC genotype of the marker g.2141C> G in the *GHR* gene was, on average, two months shorter than the interval in cows with other genotypes, and the number of C alleles showed a high correlation with the decrease in CI ($r = 0.94$, $p < 0.05$) (Table 6).

Table 6. Relationship between SNPs and increase, decrease or maintenance of the calving interval (CI) reproductive efficiency indicator for cows and heifers

Author/Year	SNP	CI/days	Effect of the association of the SNP with the evaluated characteristic
Hax et al.(25)	GHR/Alul	0,65	Maintained
Hax et al.(25)	GHR/Alul	0,69	Maintained
Hax et al.(25)	GHR/Alul	0,64	Maintained
Waters et al.(27)	GHR1.1	0,4	Maintained
Waters et al.(27)	GHR1.1	0,4	Maintained
Waters et al.(27)	GHR2.6	0,24	Maintained
Waters et al.(27)	GHR2.6	0,24	Maintained
Waters et al.(27)	GHR4.1	0,19	Maintained
Waters et al.(27)	GHR4.1	0,19	Maintained
Waters et al.(27)	GHR4.2	0,31	Maintained
Waters et al.(27)	GHR4.2	0,31	Maintained
Waters et al.(27)	GHR6.1	0,16	Maintained
Waters et al.(27)	GHR6.1	0,16	Maintained
Waters et al.(27)	GHR9.1	0,42	Maintained
Waters et al.(27)	GHR9.1	0,42	Maintained
Waters et al.(27)	AF126288:g.149	0,13	Maintained
Waters et al.(27)	AF126288:g.149	0,13	Maintained
Waters et al.(27)	GHR19.1	0,03	Maintained
Waters et al.(27)	GHR19.1	0,03	Maintained
Waters et al.(27)	F279Y	0,89	Maintained
Waters et al.(27)	F279Y	0,89	Maintained
Waters et al.(27)	N528T	0,46	Maintained
Waters et al.(27)	N528T	0,46	Maintained
Waters et al.(27)	A536T	1,06	Maintained
Waters et al.(27)	A536T	1,06	Maintained
Waters et al.(27)	H545	0,78	Maintained
Waters et al.(27)	H545	0,78	Maintained
Waters et al.(27)	S555G	0,54	Maintained
Waters et al.(27)	S555G	0,54	Maintained
Fedota et al.(28)	g.914T>A	14,3	Decreased
Fedota et al.(28)	g.914T>A	14,5	Decreased
Fedota et al.(28)	g.914T>A	13,6	Decreased
Fedota et al.(28)	g.257A>G	14,1	Decreased
Fedota et al.(28)	g.257A>G	12,7	Decreased
Fedota et al.(28)	g.257A>G	14,7	Decreased
Hax et al.(25)	IGF-I/SnaB1	66,9	Maintained
Hax et al.(25)	IGF-I/SnaB1	65,7	Maintained
Hax et al.(25)	IGF-I/SnaB1	64,8	Maintained
Hax et al.(25)	STAT5A/BstEII	64	Maintained
Hax et al.(25)	STAT5A/BstEII	71	Maintained
Hax et al.(25)	STAT5A/BstEII	64	Maintained

Single nucleotide polymorphisms (SNPs); Age at first calving (AFC).

The N° services/pregnancy was described by Bergamaschi et al.(42) as the number of matings or AI divided by the total number of cows that became pregnant. Table 7 shows this as the number of times AI was performed before the heifers or cows conceived. Analyzing the relationship between *GHR* AluI, *IGF-I*/SnaBI, and *STAT5A*/BstEII SNPs, Hax et al. (2017)(25) found no significant difference (Table 7), with an average of 2.43 N° services/pregnancy, suggesting that the use of these markers is better studied along with the productive and reproductive systems adopted on the farm. Schneider et al.(24) detected a lower N° services/pregnancy for cows carrying at least one *GHR* AluI allele and that the presence of *GHR* AluI is associated with increased concentrations of *IGF-I* in postpartum blood plasma.

Table 7. Relationship between SNPs and the increase, decrease or maintenance of the reproductive efficiency indicator number of services per pregnancy (N° services/pregnancy) for cows and heifers

Author/Year	SNP	Nº Services/ Pregnancy	Association
Hax et al.(25)	GHR/AluI	2,14	Increased
Hax et al.(25)	GHR/AluI	2	Increased
Hax et al.(25)	GHR/AluI	2,25	Increased
Hax et al.(25)	GHR/AluI	2,51	Increased
Hax et al.(25)	GHR/AluI	2,3	Increased
Schneider et al.(24)	GHR/AluI	2,75	Increased
Schneider et al.(24)	GHR/AluI	3,4	Increased
Schneider et al.(24)	GHR/AluI	2,3	Increased
Schneider et al.(24)	GHR/AluI	2,4	Increased
Hax et al.(25)	IGF-I/SnaBI	2,22	Increased
Hax et al.(25)	IGF-I/SnaBI	2,25	Increased
Hax et al.(25)	IGF-I/SnaBI	2,13	Increased
Hax et al.(25)	IGF-I/SnaBI	3,3	Increased
Hax et al.(25)	IGF-I/SnaBI	3,3	Increased
Hax et al.(25)	IGF-I/SnaBI	2,5	Increased
Silveira et al.(29)	IGF-I/SnaBI	1,4	Decreased
Silveira et al.(29)	IGF-I/SnaBI	2,7	Increased
Silveira et al.(29)	IGF-I/SnaBI	2,8	Increased
Abdolmohammadi; Zamani (30)	Transition T/C	1,49	Decreased
Abdolmohammadi; Zamani (30)	Transition T/C	1,35	Decreased
Abdolmohammadi; Zamani (30)	Transition T/C	3,11	Increased
Abdolmohammadi; Zamani (30)	Transition T/C	2,82	Increased
Leyva-Corona et al.(26)	IGF-I rs109763947	1,9	Increased
Leyva-Corona et al.(26)	IGF-I rs109763947	0	-
Leyva-Corona et al.(26)	IGF-I rs109763947	1,9	Increased
Hax et al.(25)	STAT5A/BstEII	2,16	Increased
Hax et al.(25)	STAT5A/BstEII	2,24	Increased
Hax et al.(25)	STAT5A/BstEII	2,18	Increased
Hax et al.(25)	STAT5A/BstEII	2,7	Increased
Hax et al.(25)	STAT5A/BstEII	2,8	Increased
Hax et al.(25)	STAT5A/BstEII	2,4	Increased
Silveira et al.(29)	STAT5A/BstEII	2,6	Increased
Silveira et al.(29)	STAT5A/BstEII	2,6	Increased
Silveira et al.(29)	STAT5A/BstEII	2,5	Increased
Oikonomou et al.(32)	SNP12195	0	-
Oikonomou et al.(32)	SNP12195	0	-
Oikonomou et al.(32)	SNP12195	0	-
Michel-Regalado et al.(33)	SNP12195	3,1	Increased
Michel-Regalado et al.(33)	SNP12195	2,8	Increased
Michel-Regalado et al.(33)	SNP12195	3,3	Increased

Single nucleotide polymorphisms (SNPs); Missing data (-).

The reproductive characteristics of herds are directly linked to the profitability of the system and require intense investigation to increase productivity. Kawashima et al.(43) observed that during the postpartum period, cows that ovulated earlier had higher concentrations of *IGF-I* and lower amounts of *GH* than those that ovulated later, indicating the relationship between the *GHR* genotype and its gene expression, and the concentration of *IGF-I*. Therefore, the relationship between SNPs present in genes that encode the somatotropic axis and the reproductive performance of cattle should be studied(24), especially in females that are in the first breeding season (heifers) because this information is still incomplete, and somewhat incipient in the literature.

Given the knowledge between associations with the polymorphic variants of genes involved in reproduction and phenotypic characteristics, it is possible to use selection methods and techniques involving molecular markers for improved animal productivity and efficiency(44). The frequencies of alleles and genotypes studied and used as a basis for this review(32,27,31,23,30,28,24,26,29,33) are available for consultation in the supplementary material.

Final considerations

In addition to the adoption of crosses based on phenotypes for genetic gain and increased productivity, molecular genetic techniques allow for the earlier selection of these animals based on their genotypes, thereby achieving the same objectives, with possible superior efficiency. The use of SNPs located in the genes of the somatotropic axis constitutes an important tool in the selection of bovines, as it reduces time, saves financial resources, and decreases expenses, as it allows for the identification of the genetic potential of individuals at the beginning of their lives. This information enhances the animal selection process and results in more profitable and sustainable systems.

Supplementary material

Complementary data to this article can be found online at https://revistas.ufg.br/vet/article/view/72386/38476

Conflict of interests

The authors declare no conflict of interest.

Author contributions

Conceptualization: G. S. Cruz; *Formal analysis*: R. M. S. Correa, L. L. Emerick, E. F. Castilho and M. D. N. Rodrigues; *Investigation:* G. S. Cruz, L. L. Emerick, D. B. Macedo and E. F. Castilho; *Methodology:* G. S. Cruz and D. B. Macedo; *Project management:* M. D. N. Rodrigues; *Supervision:* M. D. N. Rodrigues; *Writing:* G. S. Cruz, R. M. S. Correa and D. B. Macedo.

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