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THE IMPACT OF SELECTED SOMATOTROPIC AXIS GENES ON THE MILK PERFORMANCE TRAITS OF SHEEP, GOATS AND CATTLE

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Abstract. The aim of the present article was review of associative research concerning polymorphisms located in growth hormone receptor (GHR), insulin-like growth factor-1 (IGF-1) and Janus kinase 2 (JAK2). Improvement of ruminants production traits is closely related with identification of polymorphisms in the somatotropic axis. This genetic variation can have a positive effect on increasing milk production. The growth hormone receptor effects the metabolism of proteins, carbohydrates and lipids, while Janus kinases as transcription factors directly regulate genes involved in milk secretion in the mammary gland. Genetic factor could have a beneficial effect on increasing milk yield, and therefore, the application of marker-assisted selection can contribute to the faster identification of animals with better genetic predispositions.

Key words: ruminants, milk, somatotropic axis, GHR, JAK2, IGF-1.

INTRODUCTION

Sheep, cattle and goat farming is an important element of the world economy. Comparing 2020 to 2019, increase in world milk production, including increased international trade in powdered milk, whey and cheese, growing by 2%, while butter and skimmed milk powder had a decline in sales. Considering the increase in milk production, Asia ranked highest, followed by Europe, then South and North America, Oceania and Central America, the Caribbean (FAO 2021). The expansion of milk production in recent years was caused by a higher share of animals from which milk, meat or wool was obtained. Undoubtedly, the importance of animal products in the economy of developing countries is particular value, therefore research is carried out to identify genomic regions responsible for the performance

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characteristics of animals (Dettori et al. 2018). Identification of QTL (Quantitative Trait Loci) is statistical method with which it is easy to locate genetic markers that are linked to genes impact features of ruminants. Many QTLs have been detected with the help of microsatellite markers, but the resolution of this method is classified at a very low level, the reason is the analysis of too large a region of the genome, which also affects the potential of gene detection. A genome-wide association study (GWAS) has been developed to replace QTL. The GWAS method identifies the relationship between phenotypic features and genetic regions. This method gives the possibility of precision in narrower genomic regions. Genome wide association testing is based on single nucleotide polymorphism (SNP) in test animals. Despite the success of this technique, difficulties still exist in characterizing the GWAS associations. The use of marker assisted selection can help to speed up the identification of animals with a preferred genetic profile.

The aim of this study was to review the latest scientific literature on the relationship between somatotropic axis gene polymorphisms and the milk performance traits of ruminants, especially considering the current discoveries, in order to provide scientists with valuable support.

GROWTH HORMONE RECEPTOR

The somatotropic axis plays a significant role in the physiology of mammals. The polymorphisms contained in this axis relate to important economic features, which include synthesis, milk composition, meat production or reproductive performance. The axis consists of genes encoding growth hormone (GH), insulin-like growth factor 1 (IGF-1) and their receptors – growth hormone receptor (GHR), insulin-like growth factor receptor (IGFR), there are also intracellular signaling proteins, in which we can distinguish signal transducer and activator 5A (*STAT5A*) (Haxa et al. 2017). In mammals, growth hormone is secreted from the anterior pituitary gland trough eosinophilic cells. GH plays a key role in growth, milk production, lactation, reproductive processes, and the metabolism of proteins, carbohydrates as well as lipids (Bordonaro et al. 2020). *GHR* gene is one of the most important genes mediating the action of GH, therefore many studies have been carried out to analyze *GHR* in terms of possible polymorphisms that may affect the performance characteristics of ruminant (El-Komy et al. 2020).

The growth hormone receptor belongs to the superfamily of type I cytokine receptors, is part of the Janus kinase signaling and signal transducer and activator of transcription (STAT), also GHR has two domains, extracellular and intracellular. The bovine *GHR* gene is mapped to chromosome 20 and comprises 9 exons, located in the translation part (El-Komy et al. 2020; Cobanoglu et al. 2021). The growth hormone is connecting with GHR dimers, then a conformational change is induced, activating GH, Janus kinase 2 and downstream signaling pathways, including STAT5 (Zhang et al. 2019).

A study by Cobanoglu et al. (2021) to analyze the influence of the polymorphic site in the *GHR* gene on the dairy performance traits of Holstein and Jersey cows. The analysis included 748 specimens, including 468 Holsteins and 280 Jersey cow. A single nucleotide polymorphism (SNP) in exon 10 of the *GHR* gene was identified in them. The Holstein cows is the most frequently chosen breed in Turkey for dairy farming, while Jersey cows are bred mainly in the northern part of the country due to environmental conditions. Genotyping was performed using restriction fragment length polymorphism (RFLP-PCR). The method is based on finding differences in homologous DNA sequences. Polymorphisms are detected

based on the presence of fragments of different length after digesting the DNA samples with specific restriction endonucleases, in this case it was the *Alu*I enzyme which cuts DNA at the 5′-AG / CT-3′ site and generates blunt-ended fragments. Allele *A* presented three bands with the lengths of 191, 101 and 50 bp. Meanwhile, allele *G* resulted two bands 191 and 151 bp. Jersey cows with the *GG* genotype were characterized by a higher fat content in milk, and two genotypes – *GG* and *AG* – were responsible for a higher amount of protein. The *GG* genotype in the Holstein breed determined the highest protein content, while the *AA* genotype indicated a higher milk yield.

The genetic variability of the growth hormone gene and its receptor has been repeatedly tested and recognized as a functional marker influencing the performance traits of cattle and sheep. However, the *GHR* gene polymorphism associated with milk traits in Egyptian buffaloes was first investigated by El-Komy et al. (2020). Meanwhile, 400 individuals were analyzed, 4 SNPs were detected: c.380 *G>A* / p.Arg127Lys and c.387 *C>T* / p.Gly129 (exon 5), c.435A>G / p.Pro145 (exon 6), c.836 *T>A* / p.Phe279Tyr (exon 8). The c.380 *G>A* polymorphism affected the milk yield and the yield tested after 305 days, as well as the percentage of protein and fat, these values were higher in animals that carried the mutant A allele. The exon 8 SNP was also associated with identical features to the c.380 *G>A* polymorphism. Animals with the *AA* genotype were characterized by a higher content of tested milk components. Selection of buffalo with *AA* haplotypes can contribute to the improvement of milk quality and yield.

The sheep *GHR* gene is 167 bp long and 98.8% of the gene consists of intron regions (3038 variants reported), while the remainder of the gene consists of a missense mutation (14 variants) and a synonymous mutation (9 variants). In a study by Dettori et al. (2018) was subjected to 380 Sarda sheep, which belong to one of the main dairy breeds used in southern Europe. A custom TaqMan Real-Time PCR test was designed for genotyping. A total of 31 polymorphisms were analyzed. Rs55631463 increased the content of fat and protein in milk. The *CC* genotype was the most common among the studied individuals. The rs417647459 polymorphism in the upper *GHR* region was associated with higher lactose content. Most sheep were homozygous for the genotype. Consecutive polymorphisms: rs399882480, rs428862267 and rs402337124 had a significant effect on the content of fat, protein, casein, lactose and urea in milk.

A single nucleotide polymorphism in the growth hormone receptor gene (g.121 *G>A*) is located in exon 10 and codes for a non-synonymous mutation resulting in *AA* change from Asp to Asn. According to a study by Crisa et al. (2010) the *G* allele was associated with lower milk fat content (−0.14%). The research was carried out on 94 sheep, including 36 Altamurana sheep, 24 Gentile di Puglia sheep and 34 Sarda sheep. The *A* allele is most common in the Gentile di Puglia sheep breed, which has the highest percentage of milk fat, while the Sarda breed has the lowest fat content.

According to studies by Abousoliman et al. (2020) on 111 individuals of the Barka breed, polymorphism rs413776054 located in exon 8 of *GHR* was detected. The sheep with the *TK* genotype had the highest milk yield, while the sheep with the *TT* genotype had the highest percentage of fat, protein and lactose in milk. However, the study did not find any significant connection between the studied polymorphism and the performance traits of the Barka sheep.

In a study by Maj et al. (2007), 235 goats of two dairy breeds were genotyped: the Polish white improved breed and the Polish improved fawn breed. 10 alleles of the *GHR* gene were identified, 8 of which were characterized by a homozygous arrangement. For

the Polish White race, the frequency of the homozygous genotype was 0.25, while for the other tested breed it was 0.28. Unfortunately, wasn't found relationship with the functional properties of goat milk, such as fat, protein and lactose content.

Growth hormone receptor (GHR) was strongly suggested as a functional gene for milk quality traits (Sanchez et al. 2016). *GHR* gene mediates most functions of growth hormone (GH) such as mammary gland growth, lactation, and fertility (Lucy 2008). Several studies reported a clear association between *GHR* polymorphisms and milk production, quality, and coagulation properties (Rahmatalla et al. 2011; Viale et al. 2017; El-Komy et al. 2020).

In a study conducted by Gamal et al. (2024), on Egyptian Zaraibi goat, a positive correlation was found between the methylation pattern of *GDF-9* and *GHR* and their expression level. The breeding season was significantly effective for both peak milk yield (PMY) and total milk yield (TMY).

INSULIN-LIKE GROWTH FACTOR-1

The somatotropic axis is a major regulator of both reproductive physiology and metabolism in mammals (Jones and Clemmons 1995). Polymorphisms in the somatotropic axis genes are directly and indirectly related to the phenotype, mainly in relation to milk composition and synthesis (Song et al. 2022), meat and carcass production properties (Darwash et al. 1997) and reproductive functions (Schneider et al. 2013). One of the genes with a significant impact on the development of the milk yield of animals is the insulin-like growth factor-1 gene. IGF-1 belongs to a family of growth factors that are structurally closely related to proinsulin. IGF-1 can bind to insulin receptors and activate them. The peptide family has two members, IGF-1, the adult form, and IGF-2, mainly the fetal form. It is known that IGF-1 plays an important role in the growth and functioning of the mammary gland by regulating selected cellular processes (Akers 2006), including stimulation of protein synthesis in mammary epithelial cells. Additionally, significant associations (*IGF1i3*) with somatic cell count (SCC) were observed (Burgos and Cant 2010). Liebe and Schams (1998) found that the milk *IGF-1* concentration profile corresponded well with SCC and concluded that this is probably an important measurement in monitoring udder health. Ruffer (2003) also found that *IGF-1* concentrations increased significantly in milk collected from healthy udder quarters that were adjacent to quarters showing SCC above 100,000/ml and mastitis. Mullen et al. (2011) demonstrated the multi-faceted influence of *IGF-1* on milk production and growth-related traits in cattle. Four SNPs, all located in *IGF-1* introns, were associated (p < 0.05) with milk protein yield, milk fat yield, milk fat concentration, and somatic cell number. Mehmannavaz et al. (2010) also examined the effect of *IGF-1* polymorphism on milk-related traits in cattle, specifically in Iranian Holstein bulls. The results indicate that genetic variants in the 5'-noncoding region of the bovine *IGF-1* gene had a marked effect on estimated milk breeding values (EBVM) and fat yield (EBVF). Heterozygous bulls (*CT*) had higher EBVM and EBVF than homozygous bulls (p < 0.1).

Sebastiano et al. (2020) examined the impact of polymorphism in the *IGF-1* gene on milk performance traits in Sarda sheep. Three polymorphic sites were detected, registered at positions g184028491C>G and g184028489C>T of the 5′UTR and g184023223G>A of exon 3. The C allele at position g184028491 showed a significant association with a higher fertility rate (p < 0.05) and a shorter interval in days from introduction rams for lambing (p < 0.01). Moreover, a significant effect of the *CC* genotype on higher milk yield was found

for p < 0.05 in the second and third lactation and p < 0.01 in the fourth lactation compared to the other genotypes. Even the *AA* genotype at position g184023223 of exon 3 showed a significant effect on milk yield for p < 0.05 in the second and third lactation and for p < 0.01 in the fourth lactation compared to the other genotypes. To sum up, the identified SNPs showed a significant impact on the reproductive performance and milk yield of Sarda sheep, which suggests the possibility of their use in sheep selection plans.

The milk potential of goats is strongly related to the growth and survival of their offspring, the size of the litter is also a very important factor determining the reproductive efficiency of farm animals and has a very significant impact on the fertility of goats (Tesema et al. 2020). According to polymorphism studies, some researchers promoted the 5′-flanking region as a region influencing reproductive traits by regulating gene transcription (Rasouli et al. 2016). Furthermore, Othman et al. 2016 found a significant impact of mutations in exon 4 and introns 3 and 4 on the production characteristics of six breeds of goats and sheep bred in Egypt. Regarding the detection of *IGF-I* mutations in sheep, various studies have identified polymorphisms in the 5′ flanking region, intron 4, 5′UTR and exon 3 of the *IGF-I* gene and have shown a significant association between them and litter size and milk production traits (Lestari et. al. 2020; Sebastiano et al. 2020). El-Shorbagy et al. (2022) confirmed the impact of mutations in the *IGF-1* gene on dairy performance characteristics. They reported that individuals with the *CC* genotype had higher milk yield. Similar results were obtained by Deng et al. (2010), here also the *CC* genotype was characterized by higher milk yield than other genotypes.

JANUS KINASE 2

Janus kinase (JAK) is a non-receptor protein belonging to the tyrosine kinase family. JAKs participate in the signaling pathway as catalytic components for the following cytokine receptors: interferons, interleukins, growth hormone, leptin and erythropoietin. The Janus kinase family includes: JAK1, JAK2, JAK3 and TYK2 (tyrosine kinase 2) (Hubbard 2017). When expressed without cytokine receptors, members of the JAK family are found in the cytosol, and by binding to them, they take place in the endosomes and the plasma membrane (Yamaoka et al. 2004). JAK2 also participates in alpha and beta tubulin phosphorylation and associates with the microtubular cytoskeleton (Shahi et al. 2022).

The Janus kinase consists of four conserved structural domains (Fig. 1). At the C-terminal end of the JAK is a pseudo kinase and kinase domain. It is responsible for the enzymatic activity of the molecule. The FERM (Fourponit one, Ezrin, Radixin, Moesin Homology) and SH2 (Src Homology) domains occupy the N-terminal end and are involved in the response to receptor interactions (Ferrao et al. 2018). FERM consists of three subdomains (JH5, JH6, JH7) that structurally resemble the domains of ubiquitin, CoA, and plextrin-phosphotyrosine homology. The SH2 domain is responsible for binding phosphotyrosine residues. SH2 domain role is the activation and dimerization of STAT. The pseudo kinase domain is located in the central part of the Janus kinase, playing a regulatory role. At the C-terminal end of the JAK molecule is a tyrosine kinase, which contains an ATP binding site and a catalytic region, also the kinase is responsible for the phosphorylation of tyrosine residues (Seif et al. 2017). The *JAK2* gene in cattle is located on chromosome 8, it consists of 26 exons, which are separated at some distance by long introns. Janus kinase in sheep is located on chromosome 2, the number of exons is 25, while in goats *JAK2* takes place on chromosome 8, and is composed of 25 exons.
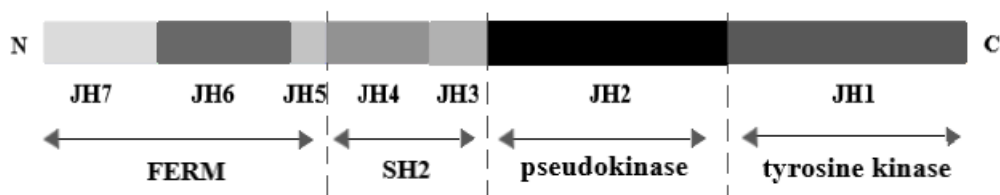
Fig. 1. Diagram of JAK domain structure (based on Santos and Verstovsek 2011)

The JAK-STAT signaling pathway is used to transmit signals from the surface of the cell membrane to the nucleus. Pathway activation go through the binding of appropriate cytokine or growth factor receptors, leading to JAK dimerization. The activated Janus kinase is phosphorylated and creates attachment sites for STAT proteins, which are also phosphorylated by tyrosine to form heterodimers or homodimers. The formed dimers penetrate the nucleus, bind to DNA and regulate the transcription of target genes (Ferrao et al. 2018; Hu et al. 2021).

Interference in the JAK-STAT pathway can lead to mastitis in cattle, resulting in a weakened immune system. *JAK2* is involved in the activation of the prolactin receptor (PrlR), which is an essential factor involved in the development of the mammary gland and the production of milk. Breast epithelial differentiation and proliferation would be 95 percent less, in the absence of *JAK2* in the perinatal period. Previous studies show that *JAK2* plays a key role in intracellular signaling during pregnancy (Shillingford et al. 2002; Khan et al. 2020). *JAK2* binds to the prolactin receptor and may enter the nucleus. Regulation of the expression of nuclear genes in the mammary gland is based on the prevention of protein degradation and the influence on the activity of tyrosine kinase (Tian et al. 2020). The JAK-STAT pathway also plays a role in the coordination of the immune system, especially cytokine receptors, and influences the polarization of T helper lymphocytes (Seif et al. 2017).

The first work on the occurrence of the silent mutation rs110298451 in the *JAK2* gene (exon 20) was published by Szewczuk (2015). A total of 904 individuals from four breeds were genotyped: Jersey, Montbeliarde, Simmental and Polish Holstein-Friesian. The relationship between the mutation in the *JAK2* gene and the characteristics of milk has been observed. It was associated with the dominance of the *G* allele in the Polish Holstein-Friesian breed, while in the jersey it was the *A* allele. The *GG* genotype in all tested breeds was associated with a higher milk, fat and protein yield as compared to the *AA* genotype.

Usman et al. (2015) detected the g.39645396 *A>G* polymorphism in the *JAK2* gene in 468 individuals of the Chinese Holstein race. A significant relationship was found with the number of somatic cells, as well as with the assessment of somatic cells in cows susceptible to mastitis. The homozygous *AA* genotype was associated with a higher level of mRNA expression. The results of published studies suggest that the discovered polymorphism in the *JAK2* gene may be a powerful marker influencing the selection of cows against *mastitis*.

In 2019 (Zahoor et al. 2019) an article was published on the effect of mutations in the *JAK2* gene on the fat content in milk and the susceptibility of Holstein cows to mastitis. At that time 312 Chinese Holstein cows were genotyped. Four polymorphisms in the *JAK2* gene were detected: 39652267 *C/T*, 39645396 *C/T*, 39630048 *C/T*, 39631175 *T/C*. A significant relationship was observed 39652267 *C/T* with SCC, 39645396 C/T with IFN-γ, IL-6 and above were connected to the fat content of milk. The 39630048 *C/T* polymorphism was associated with IL-6 and IFN-γ. The association with interleukin-6 and the percentage of fat in milk indicated SNP 39631175 *T/C*.

The polymorphisms T-C39652459 and T-C39645396 detected by Ali et al. (2020) are located in intron 15 and exon 20 of the *JAK2* gene, respectively. Milk samples and blood were collected from 201 Holstein-Friesian, Jersey and Achai individuals. The *G* allele was the most common when compared to the frequencies of the *A* allele. The homozygous *GG* genotype was associated with a higher SCC. The tested mutations determined a higher lactose content in milk.

Research by Padzik et al. (2021) show three new mutations in the *JAK2* gene in sheep. There were two polymorphisms in exon 6 (R1 = g.72850860 *G>A*; rs160146162; R2 = g.72850917 *A>G*; rs160146160), while the third was located in intron 22 (R3 = g.72895034 *G>A*; rs429445187). 64 Pomeranian sheep and 39 Suffolk sheep, 98 individuals in total, were genotyped. The homozygous *AA* genotype in the R1 polymorphism in Pomeranian sheep was characterized by the rarest occurrence, while in Suffolk sheep it was not detected. The *GG* genotype was the most common in both tested breeds. The heterozygous genotype (*AG*) dominated in the R2 and R3 polymorphisms, both for Pomeranian sheep and for Suffolk. The results presented in this study can be used in further research on the relationship between SNP and performance features.

In a study conducted by Oster et al. (2023) the influence of polymorphisms in the *JAK2* gene on selected performance traits of cattle and sheep was also investigated. For this purpose, two polymorphic sites in exon 16 and exon 23 were examined for three cattle breeds (Herford, Angus and Limousin) and three polymorphic sites, two in exon 6 and one in exon 24 for two sheep breeds (Pomeranian and Suffolk). Hereford and Limousin cattle with genotypes *AA* (e16/*Rsa*I) and *AA* (e23/*Hae*III) usually had the highest body weight and better daily gain (p ≤ 0.05). No clear trend was observed in selected reproductive characteristics. In the case of sheep, regardless of breed, individuals with the *AA* (e6/*Ear*I), *GG* (e6/seq) and *AA* (e24/*Hpy*188III) genotypes were characterized by the highest body weight and daily gain in the studied periods (p ≤ 0.01). The same individuals of the Pomeranian breed were also characterized by better fertility and lamb survival (p ≤ 0.01). These were the first association studies for all these polymorphic sites. The authors indicated that single nucleotide polymorphisms in the *JAK*2 gene may serve as genetic markers for dairy and meat production in ruminants.

CONCLUSIONS

Research shows that the genetic variability of the proteins encoded by the *GHR*, *JAK2* and *IGF-1* genes have an impact on the performance traits of sheep, cattle and goat. The detected mutations can be successfully used as markers that will be used in selection programs, with the aim of improving milk-related traits in sheep, cows and goat.

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WPŁYW WYBRANYCH GENÓW OSI SOMATOTROPOWEJ NA CECHY WYDAJNOŚCI MLECZNEJ OWIEC, KÓZ I BYDŁA

Streszczenie. Celem artykułu był przegląd badań asocjacyjnych dotyczących polimorfizmów zlokalizowanych w receptorze hormonu wzrostu (GHR), insulinopodobnego czynnika wzrostu 1 (IGF-1) oraz w kinazie janusowej 2 (JAK2). Poprawa cech produkcyjnych przeżuwaczy jest ściśle związana z identyfikacją polimorfizmów w osi somatotropowej. Ta zmienność genetyczna może mieć pozytywny wpływ na zwiększenie produkcji mleka. Receptor hormonu wzrostu wpływa na metabolizm białek, węglowodanów i lipidów, natomiast kinazy janusowe jako czynniki transkrypcyjne bezpośrednio regulują geny biorące udział w wydzielaniu mleka w gruczole sutkowym. Czynnik genetyczny może mieć korzystny wpływ na zwiększenie wydajności mlecznej, dlatego zastosowanie selekcji markerowej może przyczynić się do szybszej identyfikacji zwierząt o lepszych predyspozycjach genetycznych.

Słowa kluczowe: przeżuwacze, mleko, oś somatotropowa, GHR, JAK2, IGF-1.