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Hayvanlarda Önemli Ekonomik Özellikler için Genom Çapında İlişkilendirme Çalışmaları: Derleme

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Genomik çalışmalar
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ÖZ

Genom Çapında İlişkilendirme Çalışmaları (GWAS), çiftlik hayvanlarında üretim özellikleriyle ilişkili önemli Kantitatif Özellik Lokuslarını (QTL) belirlemek için önemli bir araç olduğunu kanıtlamıştır. GWAS, genomda bulunan Tek Nükleotid Polimorfizmini (SNP) tanımlamaya ve daha sonra tanımlanan SNP'leri ekonomik açıdan önemli özelliklerle ilişkilendirmeye yardımcı olur. Hayvan yetiştiriciliğinde süt üretimi, et üretimi, yağ ve protein içeriği, et kalitesi, yavru verimi, büyüme oranı, doğurganlık, yapağı kalitesi vb. ile ilgili birçok SNP daha önce tanımlanmıştır. Bu önemli SNP'ler koyun, sığır, keçi, tavuk, manda ve yak gibi ekonomik açıdan önemli hayvanlarda tanımlanmıştır. GWAS, bir DNA çipi yardımıyla büyük popülasyon genomlarının taranmasına ve hayvan ıslah programı için gerekli olan genomik bölgelerin belirlenmesine yardımcı olur. Belirlenen bu SNP'ler, bireysel hayvanlar arasındaki üretim farklılıklarını anlamak için bir popülasyondaki hayvanların genomları arasındaki fark hakkında bilgi sağlayabilir. İnsan nüfusundaki hızlı artış ve kişi başına düşen üretimin artması, hayvansal ürünlerin veriminde uygun bir artış gerektirmektedir. Bu önemli QTL'lerin tanımlanması, küresel gıda talebini karşılamak üzere hayvansal ürün veriminin artırılması için gereklidir. Bu derleme tavuk, sığır, keçi ve koyunlarda GWAS ile ilgili genomik çalışmalara odaklanacaktır. Ayrıca, bu çalışma GWAS'ın artan gıda talebini karşılamak için hayvanlarda önemli ekonomik özelliklerin üretim seviyesini artırmaya nasıl yardımcı olduğunu vurgulayacaktır.

Genome-Wide Association Studies for Important Economic Traits in Animals: A Review

Reviews

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ABSTRACT

Genome-Wide Association Studies (GWAS) have proved to be an important tool to identify the important Quantitative Trait Loci (QTL) associated with production traits in farm animals. GWAS helps to identify the Single Nucleotide Polymorphism (SNP) present in the genome and then correlate those identified SNPs to economically important traits. In animal breeding, many SNPs related to milk production, meat production, fat and protein content, meat quality, litter size, growth rate, fertility, wool quality, etc have been identified

(QTL)

previously. These important SNPs have been identified in economically important animals, such as sheep, cattle, goats, chicken, buffalo, and yak. GWAS help to scan large population genomes with the help of a DNA chip and identify genomic regions that are essential for the animal breeding program. These identified SNPs can provide information about the difference between the genomes of animals in a population to understand the production differences among the individual animals. The rapid increase in the human population and increasing per capita production requires a proper increase in the yield of animal products. Identification of these important QTLs is necessary for increasing animal product yield to meet the global food demand. This review will focus on the genomic studies related to GWAS in chicken, cattle, goats, and sheep. Furthermore, this study will emphasize how the GWAS has helped to increase the production level of important economic traits in animals to meet the increasing food demand.

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Introduction

The food security of the world is under threat due to rising temperatures, climate change, floods, and other environmental factors. Lower production and rising inflation are also making the price of milk, meat, cheese, and other animal products increase. The goal of today’s dairy and meat industry is to increase milk, meat, and cheese production in order to overcome the food shortage and help to reduce commodity prices. The breeding programs in the animal industry are focused on the improvement of the genetics of animals which will lead to an increase the production. Therefore, the identification of important animals that have superior genetic makeup is necessary for breeding programs (Zhang et al., 2013).

The important goal for flock improvement in animal production is to identify animals that have superior genetic makeup which can help to get better economic benefits. To achieve this goal of selecting genetically superior animals to increase flock productivity traditional breeding techniques can be combined with modern biotechnological tools (Jahuey et al., 2014). The animal genetic markers present in the DNA sequence of the animals can be identified by using DNA sequence technologies, single nucleotide polymorphism (SNP) is one of these unique technologies that can be useful to identify economically important production traits (Niño et al., 2012; Bejarano et al., 2016).

Next-Generation Sequencing gives genome-wide coverage with high-quality results, making possible the identification of mutations that can be potentially disease-related or high-risk in the genome (Ceballos et al. 2018). However, in another scenario these mutations can be signatures due to natural or artificial selection pressure or anthropogenic or evolutionary process, leading to the development of new possible lines or special breeds of animals (Boitard et al., 2016). The genome of bovine, ovine, and chicken has gone through this process of evolution and selection leading to the naturally occurring breeds. Therefore, sequencing the genomes of industrial animals like cattle, sheep, chickens, and goats and identifying these selection signatures can be helpful to identify the complex process that leads to the development of new naturally occurring breeds. Several methods and techniques have been developed to understand the process of genome modification due to evolution and selection and to identify the signature of selection and evolution. These methods use the hierarchical structure and genomic kinship between the populations to understand the relationship between different breeds (Fariello et al., 2013; Boitard et al., 2016; Yurchenko et al., 2018).

Single nucleotide polymorphism (SNP) is screened as a genetic marker in the target genes to detect changes in the phenotypic traits. These SNP can be identified in larger numbers in the target genome or a few SNPs in the single gene by using different biotechnological techniques. Genome-Wide Association Studies (GWAS) can be used to detect a large number of SNPs present in any organism's genome. GWAS has been an important tool to identify the candidate SNPs in the target potentially important genes related to many economic traits in the animal's genome. GWAS as compared to conventional techniques which are used to identify quantitative trait locus (QTL) can detect mutations in the smaller genetic range with better efficiency (Hirschhorn et al., 2005). In

the last few years, GWAS has been used in genetic selection programs involving sheep, cattle, pigs, goat, chicken, horse, and other animals, and have helped to identify many candidate SNPs in the economically important traits in commercial livestock (Gao et al., 2019: Li et al., 2019: Ghasemi et al., 2019: Liu et al. 2019). An example of one of these economic traits SNP detection in important economic traits is sheep. In sheep important genes involved in meat production, milk production, wool production, body weight, weaning weight, and yearling have been screened by using GWAS, and many important mutations SNPs have been identified in the important regions of these genes that can be used in the genetic selection program (Wei and Liu 2014).

Improving the important production trait performance in animals to gain monetary benefits, a comprehensive understanding of the genetic structure and its manipulation for phenotypic advantage is necessary. Furthermore, to underline the phenotype with genetic marker SNP short, medium, and high-density SNP panels can be used for identification and then followed by GWAS can be a complete and comprehensive strategy to increase the production performance in a genetic program in livestock (Korte and Farlow 2013). In addition, gene set enrichment, and gene prioritization analyses post-GWAS analyses have been used along with genome-wide association studies to increase the understanding of molecular mechanisms present in the genes of interest in commercial animals (Otto et al., 2020). These approaches combined helped to understand the mechanism involved around the gene working together in different biological pathways to control complex quantitative traits and help to pass the limitations of GWAS (Dadousis et al., 2017). In the dairy industry traits involving milk yield, milk fat and protein percentage and milk solids are the pivot target for breeding programs. Consequently, a large number of studies have been carried out in recent years to detect the potential QTLs by using GWAS and QTL mapping in dairy cattle (Li et al., 2020b; Otto et al., 2020), goats (Mucha et al., 2018; Guan et al., 2020), and sheep (García-Gámez et al., 2012a; Li et al., 2020a). Furthermore, many studies involving the GWAS to identify the potential SNP present in the milk-producing genes in dairy animals have successfully generated results in the genetic breeding programs (Sanchez et al., 2019; Otto et al., 2020). Present genotyping techniques can detect small amounts of low-frequency variants for separate animal breeds. These current genotyping arrays combined with GWAS provide the opportunity to identify high-priority variants in animal populations (Lee et al., 2014).

This review goes through some of the studies carried out to detect the single nucleotide polymorphism (SNP) in the economically important genes in sheep, cattle, goats, and chickens. Furthermore, this review will emphasize the importance of GWAS to detect the SNP present in the target genes for economical traits in commercial milk and meat-producing animals.

GWAS in Cattle

Increasing milk production from cattle is pivotal for some countries' dairy production sectors, therefore identifying the candidate genes involved in milk production can be beneficial to increase milk production through genetic breeding programs. Otto et al. (2020) screened the genome of Brazilian Girolando cattle to map the QTL related to milk production. Genome-Wide Association Study (GWAS) was conducted to identify the genomic regions related to 305-d milk yield in Holstein and Gir breeds. 7 candidate genes were identified on chromosomes 1, 4, 6, and 26 related to milk traits which can be targeted in breeding programs to increase milk production. A whole-genome association study was conducted to identify some candidate SNPs related to milk yield, fat yield, protein yield, fat percentage, and protein percentage in Braunvieh cattle (Max et al., 2012). Two SNPs affecting milk yield on BTA4, one SNP affecting fat percentage on BTA1, and two SNPs affecting fat yield on BTA23 and BTA14 were identified. Atashi and Hadi (2022) estimated genomic regions linked to milk production traits in Dual purpose Belgian Blue Cows by using GWAS. They were able to discover a negative relationship between somatic cell score and milk yield traits (FY, PY, MY). Gershoni et al. (2021) were able to correlate the yearling weight gain to production traits in cows the analysis showed a positive correlation of yearling weight gain with milk, protein, fat production, and cow survival while a negative correlation of yearling weight gain was seen with female fertility in Holstein cattle. Saowaphak et al. (2017) estimated Holstein cattle genomes to find candidate regions related to 305-d milk yield, length of productive life LPL, and days open. The cattle genome was genotyped by using Illumina bovine SNP50 bead chip. The GWAS resulted in the identification of 23 QTL on chromosome numbers 1, 4, 5, 8, 15, X, and 26 related to candidate genes of desired traits DOCK11, IL13RA1, SYT1, KLHL 13, GNA14, LRRC4C, and PRKG1. These QTL regions can serve the target of breeding programs to increase milk production in cattle.

Animal behavior is a complex trait that needs to be genetically characterized to develop successful breeding programs. Single-step genome-wide association study (ssGWAS) was conducted to genetically characterize the genes for yearling temperament in North American Angus cattle. The detected genes CRISPLD1, ATXN10, CAPRIN1, VAX2, FA2H, ADAM10, PLXNA1, ATP6B1V1, SPEF2, and CACNA2D3 were characterized by the complex biological processes involved in determining the social interaction, aggressiveness, and other behaviors in cattle (Araujo et al., 2021).

Longevity in cattle is characterized by two categories, part of the lifespan for early selection or the full lifespan of the animal. The data shows eight traits are connected to both categories of longevity and can be investigated to characterize the complex genetic processes involved. 150k-SNP panel was used to characterize the genome of 2630 Holstein cows from an initial group of 103,479 cows by GWAS. In total 55 SNPs located on 25 different chromosomes were identified after analysis, of these 55 SNPs 12 SNPs were seen to be influencing more than one trait. The candidate genes related to longevity and related traits identified by the study were CACNA2D1, RPRM, DNAJA3, GRIA3, FGF10, CA5A, and GTF2H5 (Zhang et al., 2021).

Meat production is a quantitative trait that is controlled by several genes. GWAS-enabled genotyping of genomic regions related to particular traits has enabled the identification of important SNPs in the genes related to meat production. Bedhane et al. (2019) screened the genome of 2110 Hanwoo cattle by GWAS to find important SNPs. The genome-wide association study identified a total of 107 significant SNPs present on the 14 chromosomes related to meat texture, fat, the color of meat, and the marbling of cattle meat. The important genes identified for these meat production-related traits were BTA2, 12, 16, 24, BTA12, 29 BTA7, 10,12, 16, 21, and BTA2, 14, 24. Pegolo et al. (2020) carried out GWAS in Piemontese young bulls to characterize carcass-related traits like carcass weight, daily gain, conformation score, and meat quality. The analyses revealed 37 different SNPs related to 12 different traits influencing the carcass and meat quality in bulls. Significant SNPs were detected on *SLC12A1*, *CGNL1*, *PRTG*(ADG), *LOC513941*(CF), *NLRP2*(CF and DP), *CDC155*(DP) genes contributing to average daily gain, carcass freshness, body weight, and dressing percentage by GWAS in Local Alpine breed (Mancin et al., 2021).

GWAS in Sheep

Sheep production is an integral part of the agricultural economy in developing countries due to important products like milk, cheese, meat, and wool. Genetic characterization and identification of SNPs in the important genes related to production traits can play a pivotal role in increasing sheep product yield by selecting animals with superior genetics. Krivoruchko et al. (2021) conducted GWAS in the Karachaevsky sheep breed to look for SNPs and genes related to production traits. GWAS was carried out by using a 600k SNP ovine infimum HD bead chip which resulted in the identification of 15 SNPs related to body size, length, and color of the coat, presence of horns, and live weight. The major candidate genes identified MAEL, EPHA4, CPT1, FCER1A, CWC27, SHISAL2B, SCIN, MYO16, and ITPKB on chromosomes 1, 2, and 21. These SNPs and genes can be a point of interest to increase the productivity of the Karachaevsky sheep breed through breeding programs. GWAS study in Churra and Spanish Assaf sheep breeds revealed 71 total genes involved with cheese and milk production traits on different chromosomes. In total 6 milk and 6 cheese traits showed significant associations with 84 to 139 chromosomal regions. The report revealed 71 possible candidate genes in both breeds that can be exploited in genetic breeding programs to increase the yield of milk and cheese-related traits (Marina et al., 2021). Bolormaa et al. (2018) investigated the reliability of previously identified QTLs in meat quality traits carcass fat depth, post-weaning body weight, post-weaning eye, and SF5 in multi-breed sheep with GWAS, the identification of new QTLs in GWAS was also conducted in their research. The data obtained by GWAS revealed new QTL regions related to meat traits and confirmed the presence of previously reported QTLs on chromosomes 6 and 18. The WGS data revealed clear evidence for the identification of old and new SNPs related to meat quality traits.

Mohammadi et al. (2022) conducted weighted single-step GWAS in Vall del Belice dairy sheep, and candidate genes associated with important economic traits were revealed e.g for somatic cell score MED28, for milk yield MYH9, PPARGC1A, LEP, and LYPLA1, protein yield and percentage ANGPT1, PCSK5, and for fat yield and percentage CACNA1C, ERCC6, CHRm3, ROBO2, and PTPN1. Krivoruchko et al. (2022) detected several SNPs which showed heavily reliable associations between the substitutions rs410503867 and rs428223899 were found on chromosomes 4 and 21, while the animals with super elite scores showed three more substitutions rs413668028, rs402746571, and rs404739757 were linked to nearby NALCN gene. The genomic associations were found in the genes NFATC2, DGKB, NALCN, PAK1, CTTNBP2, and PAK1 related to wool and meat traits in Caucasian sheep. Kizilasan et al., (2022) proposed several candidate genes (MYOM3, PRDM2, SLC44A1, PTGDR, SP1, PTPRG, TLE4, KCND2, FKBP1A, ZNF260, CPE, TMEM50A, GRID2, HCN3, SCD5, ZNF407, and SPIDR related to genetic correlation, phenotype correlation, and genomic heritability after conducting GWAS in Akkarman sheep (Yilmaz et al., 2021).

A genome-wide association study revealed significant SNPs related to body weight in Hu sheep (Cao et al., 2020). Two SNPs revealed were identified in the candidate gene CAPN6 which showed significant variants in weaned (60 days) and in 6-month-old sheep’s longissimus dorsi muscle and biceps femoris leading to marker-assisted breeding. Ghasemi et al. (2019) conducted a genome-wide association study for birth weight in meat type Lori-Bakhtiari sheep. The genotype revealed 3 significant SNPs on chromosome 1. Seven genes were identified in the genotyped regions but three genes RAB6B (a member of the RAS oncogene family), GIGYF2 (a GRB10 interacting GYF protein 2), and TF (serotransferrin) could be significant candidate genes for birth weight in Lori-Bakhtiari sheep. A genome-wide association study in Valle Del Blice sheep revealed nine significant SNPs related to milk-related traits. The SNP identified in the gene DCPS gene were found to be affecting both milk protein and milk yield, and the SNPs identified on the genes TTC7B and SUCNR1 were affecting the protein percentage and fat percentage in Valle Del Blice sheep significantly (Sutera et al., 2019). Li et al. (2020) studied the milk production traits in crossbred dairy sheep by GWAS analysis. GWAS analysis was carried out to search for significant SNPs present in the important candidate genes affecting the milk yield, fat yield, and protein yield in crossbred dairy sheep. The analysis revealed 63 SNPs each with a probability >95% and affecting at least 1one of three important milk characters. The important candidate genes were identified on chromosomes 1, 3, 4, 5, 7, and 11 which can serve as perfect targets for increasing the milk production traits' performance through genetic breeding programs.

GWAS in Goat

The goat is the oldest domesticated livestock animal that has been providing milk, fiber, and meat (Naderi et al., 2008). The largest population of the goat is found in Africa and South-East Asia where it is providing meat as the principal product (Dhanda et al., 2003). The meat demands of the world are increasing with the increasing population and to diversify the meat requirement worldwide, goat meat has been gaining importance rapidly (Pophiwa et al., 2020). Goat genetics has gone through selection pressure with human migration which has influenced the goat genetic structure a lot. The unique biological characteristics are found in the indigenous goat found in Southwest China which is house to one-third of the indigenous goats of the world (Wei et al., 2014). Mankind tends to raise those goat breeds which can provide a better yield of meat, fleece, milk, coat color, and better reproduction rate.

Inner Mongolia Cashmere goats are known for their brilliant fleece quality, and they provide better cashmere yield than other cashmere breeds (Wang et al., 2021). Wang et al. (2021) investigated cashmere yield, fiber length, and fiber diameter of Inner Mongolia Cashmere goats by using genome-wide association studies. They found 4 significant SNPs related to fleece-related traits located in regions of genes SOX5, FGF12, EVPL, and SEMA3D. Nazari-Ghadikolaei et al. (2018) reported significant markers in RALY, ASIP, AHCY, and ITCH genes associated with brown and black coat colors on chromosome 13, and white coat color associations were found on PDGFRA and KIT genes. They analyzed individual mohair traits to find genetic associations for better volume and quality of mohair. Several markers were identified on POU1F1 genes revealed associations to mohair quality on chromosome 1, for mohair volume chromosome 2 gene MREG, DUOX1 gene for yearling fleece weight on chromosome 10, for grease percentage on chromosome 7gene ADGRV1 were identified. Moaeen-ud-Din et al. (2022) identified SNPs related to growth, body weight, and body conformation traits in the goat breeds of the Punjab Pakistan genome by GWAS. Zhang et al. (2021) performed GWAS in Inner Magnolia Cashmere goats and identified 21 SNPs related to body weight in the vicinity genes LDb2, MAPK3, and LRP1B, and these may also be related to muscle growth in Inner Magnolia Cashmere goats.

Islam et al. (2020) identified six loci related to reproduction traits in goats through genome-wide association. Further analysis of their study showed five candidate genes PPP3CA, KISS1, SETDB2, KHDRBS2, and WNT10B related fecundity rates in goats. The fecundity rate variations could be related to several biological pathways shown by gene ontology studies. Guo et al. (2021) collected whole genome sequencing data from two Chinese horned and JT breeds, 14 most significant SNPs distributions showed a correlation to horn status in goats. Their study showed that the chromosome 1 genomic regions are controlling the polled phenotypes of goats. Gu et al. (2022) found 53 SNPs related to body conformation traits, bioinformatics analysis revealed a total of 42 genes SIPA1L, PSTPIP2, FIGN, C7orf57, FGF9, and CCL19, etc. were related to body conformation trait. Scholtens et al. (2020) found a cluster associated with SCS on chromosome 29 with single-SNP analysis and another cluster associated with PY, MY, and FY on chromosome 19. These genome-wide association studies show that this technique is largely helpful in finding out genomic regions related to economic traits in goats. Furthermore, GWAS can reveal many mutations in the genome that are controlling the outcome of many important genes in the goat genome.

GWAS in Chicken

The most important trait in the chicken industry economically is growth trait and is also greatly related to retail market value and breeding value (Lonergan et al., 2018). Therefore, in industrial chicken breeding identification of genomic regions related to growth traits is a pivotal component. However, the growth traits are affected by multiple genes because they are quantitative traits, which makes it difficult to identify all the genomic regions and design breeding programs to improve the growth performance by using conventional selection techniques (Zhang et al., 2021).

Recent modifications in next-generation sequencing technologies have made it possible to identify important genomic regions which are related to quantitative traits. Genome-wide association studies are one of those advancements in sequencing technologies that have made it easier to look through the genome with ease and efficiency for identifying important economic traits (Zhang et al. 2012). GWAS has made it possible to identify QTLs related to disease resistance and body weight in chickens. Many reports have identified multiple SNPs and QTLs related to BW in the chicken genome. However, chromosomes 1 and 4 are known to be associated with significant regions for BW in chickens (Liu et al., 2013; Sheng et al., 2013; Xie et al., 2012).

Dou et al. (2022) discovered at least 113 QTNs by multiple genome-wide association techniques and showed the genes GATA4, ACTA1, GPR39, IGF2BP1, APCDD1, TAPT1, BAMBI, LDB2, INHBA, PRKCA, SLC16A7, TGFBR2, and GLI3 were related to rapid body growth in chicken. Mebratie et al. (2019) discovered 21 SNPs, and 11 QTLs significantly related to body weight while 5 SNPs and 5 QTLs were found to be related to FE traits. Habimana et al. (2021) discovered 4 SNPs (rs14123334, rs74098018, rs314702371, rs13792572) related to body weight traits on chromosomes 8, 11, and 19. Furthermore, 4 genes MRM1, PBX1, MPHOSPH6, and GPATCH1 were identified in the vicinity of the above-mentioned SNPs. Yang et al. (2021) discovered 25 INDELs and 134 SNPs strongly associated with five comb characters in chicken. The INDEL and SNP-based GWAS showed a region on chromosome 6 significantly associated with the comb trait, one lead INDEL, and 2 SNPs were detected on this chromosome. Additionally, they were able to identify 2 more candidate genes for comb development.

Gao et al., (2022) identified 37 SNPs situated in the vicinity of economically important genes like TTLL, GAL, SLIT3, TFAP2D, PSMB2, CPQ, NCALD, and SLC5A7 related to eggshell thickness, egg weight, Haugh unit weight, body weight, first oviposition, and eggshell strength. Wu et al. (2022)

performed GWAS in Yandang chicken and were able to find one SNP related to keel length. Furthermore, on chromosome number 5 CYB5R2 and FGFR2 related to cell proliferation and migration were identified by using INDEL-based GWAS.

The identification of important SNPs related to economic traits in livestock and other commercial animals can help to assist the breeding programs focused on increasing the yield of animal products. GWAS can help in identifying the significant QTLs and SNP related to commercial traits the meat production, milk production, fecundity, egg laying, live growth, milk content, meat quality, and other important economic traits of commercial animals in the world.

Conclusion

The number of studies using Genome-wide association studies GWAS to analyze the livestock genome has increased in the previous years. The results and findings of these studies provide a serious positive case for the continuation of GWAS for discovering the important SNPs and QTLs related to economical traits in farm animals. Improving the genetics of livestock will not only increase the food production of the world it would also help to increase the farmer's income. GWAS provides promising results which can be employed to increase the genetic potential of farm animals. Though further validation is needed with each of these genetic markers, the current results look very promising for making a positive impact on producers' profits.

Conflict of Interest Declaration

The authors of the article declares that there is no conflict of interest.

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