Genome-wide association studies in sheep from Latin America. Review

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Abstract:

Sheep are one of the most important domestic species worldwide due to their productive and reproductive potential. Therefore, identifying the best animals with productive characteristics of economic interest is the main goal in flock breeding programs. However, in most of Latin American countries, animal selection is inefficient due to subjective selection and the complex nature of these characteristics; given their quantitative nature, their expression involves the interaction of multiple genes with the environment. Currently, due to the advances in new sequencing, genotyping, and genome-wide association studies (GWAS) technologies, it has been possible to identify numerous variations in the DNA of animals, mainly single nucleotide polymorphisms (SNP) that can be found in genes that affect the expression of traits of economic interest. This review presents the progress in implementing genome-wide association studies (GWAS) in Latin America, their use in sheep production systems, and the results obtained in productive, reproductive, functional, or quality traits.

Key words: Candidate genes, GWAS, Breeding, Phenotypic traits, Genotypic traits, SNP.

Introduction

Sheep are one of the most distributed species worldwide; they live in every climate and ecosystem[1]. In Latin America, there is an estimated population of 80 million heads, most in countries like Brazil, Argentina, Peru, Bolivia, Mexico, and Uruguay[2], making their breeding an activity of great economic and food impact in indigenous communities and small farmers[3]. In these regions, systems are characterized by using creole ecotypes and traditional handling, which makes them less competitive against Asian and European countries, profiled as the main meat, milk, and wool producers[4,5].

Currently, one of the main goals to improve flock production in Latin America is to identify and genetically improve superior animals for economically important traits; it has been recognized that one of the alternatives to increase flock productivity, through selection, is the use of biotechnological tools that combine traditional breeding techniques with molecular information[6]. These tools involve DNA sequencing technologies, which allow identifying a considerable amount of animal genetic markers, especially single nucleotide polymorphisms (SNP), which can affect important productive traits[7,8].

Therefore, genomics has begun to impact the genetic study of production animals through methodologies such as genome-wide association studies (GWAS), which use the information from thousands of SNP distributed throughout the entire genome and from the estimation of their effects to select and identify regions or loci involved in the variation of quantitative traits (QTL)[9]. These markers are used to define candidate genes where those nucleotides that influence phenotypic variation (QTN) are located and discover the molecular mechanisms that direct the expression of complex traits in domestic species[10,11]. In sheep, GWAS have mainly focused on the study of productive and some phenotypic traits, such as coat color, presence or absence of horns, among others[9].

Current state of sheep in Latin America

The importance of sheep as a domestic species lies in their high productive and reproductive potential, since in addition to using ecosystems that are not useful for other species, a greater number of animals can be bred per unit area, they have a short generation interval, high prolificity, high growth rates, and good feed efficiency; they are excellent weed controllers, and added value can be obtained from dairy and meat products[12-14]. As with other economically important species, sheep result from the domestication of wild species, the majority coming from the Middle East in the so-called Fertile Crescent of Asia[15,16]. Due to evolution and human selection, there is a great variety of breeds worldwide with traits and aptitudes for different types of production[17].

The racial base of wool and hair sheep in Latin America is composed mainly of genotypes brought during the colonization era, which were bred without any reproductive order more than 500 years ago; this situation produced a miscegenation that lasted for centuries and that gave rise to a variety of sheep adapted to different ecosystems and the special conditions in each region, called creole[16,18,19]. In Latin America, most of the sheep population is creole, except for Argentina, Chile, and Uruguay whose population is mainly composed of improved animals imported from Australia and Europe. Creole sheep constitute an important zoogenetic resource for Latin America because they are animals adapted to the tropical environment, prolific, and easy to handle; additionally, they play an important social and economic role, as they guarantee food security and economic income to marginalized and extremely poor populations[13,14,18].

In recent years, the sheep population in Latin America has been fluctuating, going from having, together with Oceania and Europe, more than 60 % of the population in the 80s and 90s to currently having less than 30 %[20,21]. The population of Latin America participates with 6.4 % of the total population in America, with the highest number of animals in Brazil, Argentina, Peru, Bolivia, Mexico, and Uruguay (Table 1)[2]. The decrease in this type of sheep is mainly due to the lack of information about these animals and the fact that producers have limited themselves to using foreign breeds for absorbent crosses, under the assumption that the productive performance of these cattle is better, which has threatened the genetic wealth of these sheep, endangering their conservation[22,23].

Table 1: Sheep heads in Latin America (2014-2019)

Country	Sheep population
Brazil	17'976,367
Argentina	14'866,000
Peru	12'415,395
Bolivia	9'499,147
Mexico	8'575,908
Uruguay	6'567,000
Cuba	2'173,400
Chile	2'037,516
Colombia	1'578,684
Ecuador	739,475
Guatemala	692,900
Venezuela	550,000
Dominican Republic	123,000
Costa Rica	35,800
Panama	18,665
Honduras	16,000
Nicaragua	13,800
El Salvador	11,493
Puerto Rico	10,759

Adapted from[2, 21].

In Latin America, sheep production systems generally develop with wool and hair animals, obtaining from the first milk and its derivatives, wool, and artisan products, and from the second meat products and female breeding stock, some producers are engaged in both activities[24,25]. The main meat producing countries in Latin America are: Brazil with 21.13 %, Mexico with 14.26 %, and Argentina with 12.05 %; while the main wool producing countries are: Argentina (30.59 %) and Uruguay (24.47 %). Moreover, in America, sheep milk production represents only 0.9 % of the world total. FAO reported for 2017 the following production data: 57,754 t for Mexico, 35,000 t for Bolivia, and 4,300 t for Ecuador[26].

There are different production systems with specific characteristics, highlighting mainly the intensive, extensive, and semi-extensive systems; the intensive system is characterized by the use of advanced technologies and improved breeds such as Texel, Ile de France, Suffolk, Hampshire, and Dorper in Brazil; Merino, Corriedale, Rommey Marsh, Lincoln, Frisona, Manchega, and Pampinta in Argentina; Black Belly, Charollais, Dorper, Dorset, East Friesian, Katahdin, Cubano Pelibuey, Rambouillet, Romanov, Saint Croix, Damara, and Texel in México, among others; in the intensive system, the productive and reproductive indices are better than in the extensive and semi-extensive systems[27]. The extensive system

is characterized by the use of creole animals or their crosses with improved breeds, located in large areas of land, generally with low agricultural capacity and few handling practices[3]. Finally, semi-extensive systems possess characteristics from the intensive and extensive systems; animals graze and are also fed with forage, alternate protein concentrates or banks; in this system, animals are generally bred for dual purposes, for meat and milk production or meat and wool production, the productive parameters are better than those from the extensive system[12]. The main creole ecotypes used in semi-extensive and extensive systems in Latin America are: Morada nova and Santa Inés in Brazil[28-30], Pantaneira in Argentina and Brazil, Junin, Piura, Criollo de la Sierra and Criollo de Arequipa in Peru[31], Pelibuey in Cuba and México[32,33], Etíope and Sudan in Colombia[34-36], Ovino Criollo Uruguayo in Uruguay[37], Ovino Criollo Araucano in Chile[38], among others.

Genome-wide association studies GWAS and their use in sheep

GWAS are a relatively new technology in sheep; they were initially used in human medicine and genomics as a tool to characterize and find variants associated with pathologies or predisposing to their development[39]; also applied to know existing gene interactions, their modification and to detect high-risk haplotypes or combinations of multiple SNP within a single gene[40]. Due to the popularity of these studies in humans, their use expanded to animal medicine and production[41], where they are a useful tool to identify genes or genomic regions responsible for the genetic variations in the most important productive traits[10,19,40,42].

In sheep, GWAS have quickly evolved in domestic and wild ecotypes due to the collaboration and benefits of projects led in recent years by institutions such as the International Sheep Genomics Consortium (ISGC, http://www.sheephapmap.org), the European Bioinformatics Institute (EBI), and the Baylor College of Medicine Human Genome Sequencing Center, who sequenced the genome of the domestic *(Ovis aries)*, wild *(Ovis aries musimon)*, and some economically important breeds such as Rambouillet[43]. Currently, this information is in public databases such as NCBI, ENSEMBL, and UCS, and different versions of the domestic sheep genome can be found, Ovis_aries_1.0 (2010), Oar_v3.1 (2012), and Oar_v4.0 (2015); these data have made it easier for the scientific community to popularize the use of GWAS in different fields[44].

The use of this technique in sheep has also been possible due to the development of large collections or panels of molecular markers known as microarrays or DNA chips, which allow to identify and explore the genome in search of polymorphic regions or markers associated with traits of productive interest[10,45]. Overall, the polymorphisms included in these panels are the SNP, since they represent the highest genetic variation in an individual, they are the

most common in the genome, and can be located in different areas of the genome: both in regions that preside over RNA codification and replication control, such as promoters, microRNA target zones, and protein-coding regions; they also have a low mutation rate, low levels of homoplasy, and are easy to genotype[7,46-49].

Commercial houses like Illumina and Affymetrix, together with the Sheep Genomics Consortium, and other entities around the world have developed genotyping matrices with different types of coverage within the genome. Illumina features: Ovine Infinium® HD SNP BeadChip, Ovine SNP50 BeadChip, OvineLD BeadChip with probes directed to 606.000, 54.241, and 15.000 SNP and high, medium, and low coverage, respectively. Affymetrix features the Axiom™ Ovine Genotyping Array with medium density and coverage of 54.236 SNP[50]. Currently, the most used chip in sheep is the OvineSNP50, which was designed with more than 3.000 samples from 75 breeds of domestic sheep (*Ovis aries)* and wild species such as mouflons *(Ovis aries musimon)*, North American bighorn sheep *(Ovis canadensis)*, thinhorn sheep *(Ovis dalli),* Asiatic urials *(Ovis vignei)*, and argali *(Ovis ammon)*[19,51-53]. With this chip, 12 samples can be simultaneously analyzed in a micro-matrix with the 54.241 probes; each matrix is of medium density because the average distance between each SNP in the genome is 50.9 kb[54]. The first GWAS in sheep aimed to identify the genetic structure of the polymorphisms associated to the presence or absence, and type of horns in wild sheep phenotypes; these studies found that by analyzing the genome with 36.000 SNP, the main candidate gene for the horn trait was RXFP2, an autosomal gene with a known implication in determining the primary sexual characteristics in humans and mice[43]. Moreover, Zhao *et al*[55] performed a GWAS to search for causal mutations in the genome of Corriedale sheep with rickets and found that the R145X mutation in the DMP1 gene was responsible for the appearance and inheritance of this pathology.

Other studies have been performed to elucidate the phylogenetic structure of sheep populations and the result of centuries of evolution, Kijas *et al*[53] found the relationship, in terms of divergence times, between 74 breeds of sheep estimated from the haplotype exchange[44]. In 2012, they identified 31 genomic regions that contain genes for coat pigmentation, skeletal morphology, body size, growth, and reproduction[53].

Nanekarani *et al*[56] reported that the Calpastatin (CAST) and Callipyge (CLPG) genes were associated with meat quality traits; for example, animals that express the Callipyge gene have higher percentages of muscle deposition, a greater loin eye area, and leaner meat. Guðmundsdóttir[42] found 13 candidate genes for muscle formation in Icelandic sheep: SF3R, ADAM17, GADD45B, GRID2, SPG11, DAB2, FREM3, GAB1, KLF13, AKAP6, PNN, DOCK1, TRRAP, and GADD45B.

Other authors[57] focused on the functional mechanisms that regulate the production of glucocorticoids induced by stress and their effect on the health of sheep; their study consisted in identifying key genetic aspects that influence the cortisol response to a bacterial endotoxin-induced stress model (BEIS)[57]. Results showed that 16 SNP were significantly associated with the cortisol levels; these SNP were located near important genes like CD14, ITGAM, ITGAL, and SNX2.

Aali *et al*[58] studied the relationship between the polymorphisms in exon 6, the intronic limits of the CAST gene, and the fatty acid profiles, the physicochemical composition, and the quality characteristics of the muscle *Longissimus dorsi* (LD); they found that the selection of lambs with the "I" genotypes, the CAST-10 haplotype, the "AA" genotype of SNP G62A, and the "GT" genotype of SNP G65T results in a greater proportion of healthy fatty acids and more tender meat[58]. Other researchers[59] studied the body size of Frizarta dairy sheep and found evidence about the influence of 39 genes on this trait, including some previously described in other studies and some new ones such as TP53, NTN1, and ZNF521. In France, they analyzed the structure of a population of 547 sheep and found selection markers such as ABCG2, LCORL NCAPG, MSTN, and genes involved in coat pigmentation (ASIP, MC1R, MITF, TYRP1, EDN3, and BNC2), height and morphology (NPR2, MSTN (GDF-8), LCORL, NCAPG, ALX4, and EXT2), milk production (ABCG2), horns (RXFP2), and wool (IRF2BP2)[60].

GWAS in sheep in Latin America

In Latin America, traditional breeding techniques are still the most widely used in most species; these are based on the identification and selection of superior individuals based on the phenotypic expression of the traits of productive interest[61]; the results from these techniques allow to characterize and categorize animals from the estimation of population genetic parameters such as heritability (h^2), genetic correlations, variances ($\sigma2$), and covariances[46]. From these data, it is possible to identify and evaluate the polymorphisms of the gene sequences that may have effects on productive traits and thus carry out evaluations in which molecular information is incorporated into the evaluation models of productive data, generating as a result more precise genetic parameters[8]. Therefore, the trend in some countries is to use tools such as GWAS that combine the use of genomic and genealogical information, production records (detailed information on the activities performed in production systems), and phenotypic traits (any detectable trait of an organism (structural, biochemical, physiological, or behavioral, determined by an interaction between its genotype and its environment) to improve the estimation of genetic values for complex traits, such as

growth, prolificity, meat quality, among others[7].

The reports of GWAS in sheep are few compared to the ones performed in cattle and pigs, finding that most of the studies in sheep correspond to Brazil[29,30,62], Colombia[23,34,63], Chile[38,64], and Uruguay[65]. These studies have focused on finding genes related to growth, an important trait associated with meat production, which has an economic impact on the producer and the industry. In Colombia, they studied the genetic variability of 23 SNP from creole sheep and found that 21 were located in genes with known functions and two in proteins not yet characterized; these and their different loci are related to the immune system and growth (muscle and bone formation)[66] (Table 3). Moreover, the genome of a population of creole Camuros genotyped with the OvineSNP50 BeadChip was evaluated to establish the relationship between the genetic component and the tenderness of the meat from the *Longissimus dorsi* muscle[63], finding a significant effect of three SNP located in the OAR3, OAR4, and OAR9 chromosomes; the OAR3_130491628.1 SNP, whit a [C/T] nucleotide change, is associated with an exonic portion of the MGAT4C gene, which has been mapped in the q arm of the chromosome, close to the DCN (Decorin) gene responsible for collagen degradation postmortem. The OAR4_118954127.1 SNP, whit a [A/G] nucleotide change, is not associated with any specific locus, but the s43296.1 SNP, in the chromosome 9 and with a [A/G] nucleotide change, was found associated with a locus not yet characterized. A different GWAS associated the muscular growth and carcass quality traits in Colombian, Ethiopian, Sudan, and Pelibuey hair sheep in the Cesar, Córdoba, and Valle del Cauca departments, finding eight candidate genes (SLC44A3, PAM, CEP135, EMCN, PRDM13, BEND3, CHAMP1, and PIAS2; Table 2) related to cellular growth, apoptosis, and angiogenesis; additionally, this association allowed to identify differences between the breed varieties despite that in Colombia, the Ethiopian and Sudan sheep are not yet recognized as breeds[34]. Lenis found polymorphisms in the SNP of the CAPN, CAST, LEP, GH, and IGF-1 loci (Table 2), as well as a significant association between the CAST gene and the PN trait in creole sheep absorbed by Pelibuey. A study similar to the previous ones, but in Uruguay, reported SNP located within genes associated with growth, meat and carcass quality PPARGC1A, DGAT1, CAST, GHR, GHRHR[67](Table 2).

Table 2: Genes reported by some Latin American authors for economically important traits

Gene	Trait	Author	Country
CYP11A1, CYP1A1, CYP19, SFXN1	Transport and construction of iron molecules, indicator of anemia.	Berton *et al*., 2017	Brazil
B2M, SFXN1, IL25, BMP4, TSHR, CCL28, PIK3R1, FGF10, IL15, IL2, TP-1, BPMG, BCL10, HSPD1, MALT1	Immune response and defense of the body		
ADAM10, IL6ST, TNFRF13B, SIVA1, JUN, PAX1, PIK3R1, SIT1, AKT1	T cell differentiation		
SLC44A3, PAM, CEP135, EMCN, PRDM13, BEND3, CHAMP1, PIAS2	Growth and carcass quality	Palacios, 2018	Colombia
NPAS2, MRPS30, TPH2, TRHDE, CDH12, PARP14, DGAT2, WNT11	Saturated fatty acid profile	Rovadoscki, 2017	Brazil
COPB2, DGAT2, ALCAM, PARP14, TPH2, TRHDE, FOXO3, OSTM1,	Monounsaturated fatty acid profile		
TPH2, TRHDE, TNFAIP8, UBE3D, ME1, PLCXD3, C6, C7, CCDC88C, FBLN5, CACNA1C	Polyunsaturated fatty acid profile		
DGAT2, TRHDE, TPH2, ME1, C6, C7, UBE3D, PARP14, and MRPS30	Fat composition	Rovadoscki *et al*., 2018	Brazil
GDF9, BMPR1-B, BMP15	Prolificity	Lacerda, 2016	Brazil
TNNT2, HTRA3	Adult weight	Amorim *et al*., 2018	Brazil
CARTPT, PIK3R1, GHR	Maternal ability		
MSX1, DRD5,	Maternal metabolic efficiency		
SLCO4C1, OOEP, GATA6, CUL4A, ZFAND5, OPEP, PAGS	Twinning		
LDHA, MYC, BHLH, MDFIC, MSTN	Adult metabolic weight		

AOX1, LTBP1, PAK1, THRSP	Body condition score		
ADAMTS12, AMHR2, AQP3, ARHGAP24, C6, C9, COL1A1, COPS7B, DAB2, DROSHA, FGR, FYB, GDNF, GOLPH3, GPR158, GPR65, IL1RL1, KR8, MACROD2, MAPKAP1, MSRB3, NIPBL, PIK3CB, PLCB1, SKAP2, SMAD6, SNX27, SPEF2, TRPM8	Immunity	Simoni Gouveia *et al*., 2017	Brazil
CNTNAP2, FUT9, GDNF, ISPD, LIFR, MACROD2, MAPKAP1, NIPBL, CPLPP.P	Nervous system development		
COL1A1, NIPBL, PDE6D, and TRPM8	Sensory perception		
AMHR2, KRT8, NIPBL, PLAG1, PLCB1, RXFP2, SP1, SPAG6, and SPEF2	Reproduction		
CAPN, CAST, LEP, GH, and IGF-1	Growth	Lenis, 2019	Colombia
UBE2N, SOCS2, LAMC1, EPS15, ATP2B1, LRP8, GALNT4, MUC15	Immunity	Benavides *et al*., 2015	Brazil
CAST, GHR, DGAT1, SERPINA3, GHRHR, HSPB1, DGAT2, SCAP, SCD5, ITGB1,	Carcass quality, growth, and meat quality	Armstrong *et al*., 2018	Uruguay

In Brazil, main sheep meat producer in Latin America, studies have focused in improving the nutritional aspects of the final product, such as the fatty acid profile and the meat quality; therefore, Rovadoscky[29], by analyzing genotypic and phenotypic information of Santa Inés sheep found 28 candidate genes associated with the mentioned traits, of which only the DGAT2 and TRHDE genes are annotated and related to the fatty acid profile (Table 2). Rovadoscki and other researchers studied the genetic architecture of the composition of fatty acids in the *Longissimus dorsi* muscle in Santa Inés sheep, finding genetic variation for the evaluated traits; therefore, it is possible to alter the fatty acid profiles through selection[30]. From the GWAS they obtained ten SNP associated with 27 genomic regions that influence the composition of fatty acids, these were located on the 1, 2, 3, 5, 8, 12, 14, 15, 16, 17, and

18 chromosomes; these regions correspond to 23 genes, among which are DGAT2, TRHDE, TPH2, ME1, C6, C7, UBE3D, PARP14, and MRPS30 (Table 2).

Another characteristic of economic importance studied in Latin America is prolificity. In Chile, researchers studied the size of the litter through the BMP15 and GDF9 genes in the Araucana creole sheep, one of the most important zoogenetic resources for farmers in the Mapuche ethnic group. For the GDF9 gene they found eight SNP, seven previously documented for this gene and a new one, called FecGA; of the SNP, c.978A and c.994G are fertility genetic markers in Araucana creole sheep[38]. The polymorphisms of the BMPR1B, BMP15, and GDF9 genes were previously studied in three creole sheep breeds; Chilota, Araucana, and Austral; the FecG1 allele was associated with the litter size in the three breeds[64] (Table 3).

Table 3: Summary of genes reported by different authors in Latin America

SNP	OAR	Gene	Trait	Author	Country
G1	5	GDF9	Growth differentiation factor-9	Paz *et al*., 2014	Chile
FecBB	6	BMPR1B			
FecXI, FecXB, FecXH, FecXG	X	BMP15	Litter size	Bravo *et al*., 2016	Chile
FecGH, FecG1	5	GDF9	Prolificity		
FecXG , FecXL	X	BMP15	Multiple birth	Argüello *et al*., 2014	Mexico
OAR18_52089434.1	18	SLC44A3, PAM, CEP135, EMCN, PRDM13, BEND3, CHAMP1, and PIAS2	Birth weight, year weight, pre-weaning gain, loin eye area, carcass compactness index, and cold carcass weight	Palacios, 2018	Colombia
OAR5_37738161.1	5				
OAR8_87794040.1	8				
OAR14_14650208.1, s50332.1, s26449.1, s72056.1, s56356.1, OAR14_15968361.1	14	MC1R	Coat pigmentation		
OAR10_55949918.1	10	SPRY-2	Myogenesis	Muniz *et al*., 2016	Brazil
s11567.1	14				
OAR3_56021384.1	3	CDH13	Melanoma		

OAR7_82985623.1	7	YLPM1	Cellular apoptosis		
OAR21_52583090.1,	21	KAPS			
OAR12_17005059.1	12	CAPN2	Endoparasite resistance	Biagiotti, 2016	Brazil
OAR8_91253490_X.1	8	QTL-OPG			
s23985.1, OAR2_148350187.1,	2	QTL-CE			
s26633.1	6	SPP1			
OAR1_189179554.1		CD200			
OAR1_23734999.1	1	LOC105605154			
s12060.1		PLPPR4			
s25125.1		PDE4DIP	Growth	Noriega et al., 2018	Colombia
OAR2_96008804.1	2	MTAP			
OAR3_61737307.1		RFN103			
OAR3_89348294.1	3	TMEM178A			
s62226.1		RDH14			
OAR5_107977075.1	5	PAM			
OAR5_112451694.1		EFNA5			
s11274.1		GABRG2			
OAR6_27552838.1		EMCN			
OAR6_77919148.1	6	CEP135			
OAR7_85269064.1	7	CIPC			
OAR8_39977285.1		PRDM13			
OAR8_50320412.1	8	MAP3K7			
s33129.1	9	CNGB3			
OAR10_59207797.1		SLITRK1			
OAR10_91128145.1	10	CHAMP1			
OAR12_20575087.1	12	USH2A			
s01263.1	14	LOC101113879			
OAR23_49635171_X.1	23	PIAS2			
DU261801_281.1	26	PSD3			
OAR3_130491628.1	3	MGAT4C	Meat tenderness	Ortiz et al., 2015	Colombia

In Brazil, prolificity (number of lambs born per ewe) was studied through genomic association in sheep of the Morada Nova breed, finding that the GDF9, BMP15, and BMPR1-b genes express in multiple birth animals[62] (Table 2). With the SNP obtained in this study, a low-density panel was performed for prolificity, after being validated in sheep of prolific breeds with a history of single and multiple calving. Amorim *et al.*[68] studied prolificity in Santa Inés sheep. After performing GWAS for maternal efficiency, maternal metabolic efficiency, twinning, adult weight, adult metabolic weight, and body condition score variables, they found six common candidate regions. Moreover, for adult weight and adult metabolic weight, 15 regions were found in common, and finally, adult weight and body condition coincided in a region located on chromosome 21. The only trait that was not related to the other variables was twinning. Among the genes found in chromosomes 16 and 5, CARTPT, MSX1, DRD5, SLCO4C1, OOEP, GATA6, CUL4A, ZFAND5, OOEP, TNNT2, LDHA, MYC, and MDFI were identified; as associated with appetite regulation, energy balance, maintenance of body weight and stress response, muscle growth, embryonic development, reproductive behavior, membrane transporters, progesterone secretion, oocyte maturation and oogenesis, subcortical maternal complex, muscle contraction, calcium regulation, glycolysis and transcription regulation. In Mexico, the FecXG and FecXL polymorphisms of the BMP15 gene (Table 3) were reported for the first time in Pelibuey sheep; after the GWAS, they found that the homozygous genotypes of these polymorphisms were related with a higher number of lambs, as there were more double births[32].

In Latin America, one of the main causes that affect the efficiency of production systems is parasitic infestation; animals that are less resistant and adapted to environmental conditions are more susceptible to lose weight and even die, since they do not recover from the parasitic infestation. Therefore, some genomic association and selection studies in breeding programs have focused on finding and selecting animals that show resistance to gastrointestinal infection by parasites. Biagiotti[69] performed a GWAS to evaluate the resistance to parasites in Santa Inés sheep and found SNP (Table 3) significantly associated with body condition score in chromosome 2, tremors in chromosome 21, and presence of *Strongylus* eggs in chromosomes 8 and 12. Subsequently, in sheep from the same breed, they also studied the resistance to parasites, particularly to *Haemonchus contortus*, using a low-density panel (SNP12k BeadChip) of 12.785 SNP, where several candidate genes were located in the chromosomes OAR1, OAR2, OAR3, OAR5, OAR8, and OAR15, related to the development and activation of the immune system, inflammatory response, and regulation of the proliferation of lymphocytes and leukocytes[61]. These genes (Table 2) can assist in selecting animals with greater resistance to parasites, and the BeadChip Ovine SNP12k could be a useful tool to identify genomic regions associated with traits related to the resistance to gastrointestinal parasites.

In a different study, after performing a GWAS to determine an association between resistance to parasites and type of host in Maasai and Dorper sheep adapted to the tropical environment of Brazil, where extreme exposure to the parasite is constant, especially *Haemonchus contortus*[70], candidate immune variants were found for genes involved in response to infection, as well as additional information on SNP useful for selection by resistance to gastrointestinal parasites in sheep with a genetic background similar to the population studied. Among the genes that were found are: UBE2N, SOCS2, LAMC1, EPS15, ATP2B1, LRP8, GALNT4, MUC15 (Table 2).

Periasamy *et al*[71] performed a study in 713 non-related sheep, involving Junin, Corriedale, and Pampinta sheep from Peru and Argentina, respectively; they identified 41 SNP in 38 candidate genes, associated with resistance to gastrointestinal nematodes. Other parameters are related to phenotypic characteristics such as coat color, breed assignment, and population structure; important in selection programs aimed at pure individuals, such as the case of the Morada Nova hair sheep in Brazil, which presents white and red animals recognized by the Brazilian Association of Sheep Breeders, but there are other black color variants with pigmented noses that are not accepted in genealogical records and some studies suggest that they are similar. Other researchers[72] performed a GWAS to identify genomic regions associated with the coat color and confirm that the black sheep are similar to other varieties of Morada Nova; their results show that the differences between the black and red coat sheep result from the expression of different alleles of the same gene (MC1R located in the OAR14 chromosome) without directly affecting the productive/reproductive traits. Moreover, they concluded that these two varieties showed low genetic variation, insufficient to consider them different groups.

In Uruguay, researchers studied the genetic diversity of three sheep breeds (Corriedale, Merino, and Criolla) to confirm the breed assignment and analyze the population structure of commercial and creole breeds; their results show that when using a subset of 18.181 SNP, the principal component analysis and the STRUCTURE yielded the stratification of the population within breeds[52]. The divergent lines of Merino and Corriedale showed high levels of polymorphism (89.4 and 86%, respectively) and a moderate genetic differentiation between them (Fst= 0.08). However, creole sheep only had 69 % polymorphic SNP and showed greater genetic differentiation (Fst= 0.17) with the other two breeds. In Brazil, a similar study was performed in the Brazilian creole sheep breeds Morada Nova and Santa Inés to find genomic regions that may have been under selection and therefore explain the ecological and production differences observed between the three breeds[19]; Table 2. The performed analyzes allowed them to identify 86 candidate genes; the functional analysis revealed genes related to immunity, nervous system development, reproduction, and sensory perception, some of the genes are of particular interest, including: RXFP2, which was recently associated with the presence/absence and morphology of horns in sheep; the TRPM8 gene, involved in body temperature regulation at low temperatures; DIS3L2, PLAG1, and

NIPBL, associated with height variation; and finally, SPEF2 and SPAG6, important for spermatogenesis. De Simoni Gouveia *et al*[19] also found specific signals of each breed, which are related to the adaptation to the environmental conditions of Brazil.

Advantages and disadvantages of GWAS and genomic selection

GWAS and tests based on genomic information allow the selection of the best animals and increase their breeding efficiency[9,10] through the exploration of the Linkage disequilibrium, that is, the association between genes that is not a product of chance due to the proximity of these in the same chromosomal segment[73-75]; and a large number of SNP markers distributed throughout the genome[9,72]. In this way, the sum of all the small effects of the SNP will allow predicting breeding values with greater precision, by recovering the favorable haplotype combinations for the traits of interest throughout the genome[33,42] and identifying genes that affect the production traits in domestic animals[43,72,76].

In genomic selection, the most favored traits are those with low heritability and that are strongly influenced by the environment (birth weight, weaning weight, age at first calving, calving interval, and daily weight gain at weaning, among others)[34,36,77], which represents an important advance in the genetic improvement of animals since there is greater control of genetic aspects and environmental effects are separated. Regarding traits that are difficult to measure, the selection from genomic information is a disadvantage since the availability to discover new variants or validate those that already exist requires infrastructure, resources, significant samples, and, above all, the generation of phenotypes[33].

Genomic information can also help identify individuals who carry congenital defects, with the SNP50 BeadChip in GWAS, the genes responsible for many sheep diseases, such as microphthalmia[78], epidermolysis bullosa[79], rickets[55], ovine lentivirus[75], and chondrodysplasia[80], have been successfully identified. Identifying the carrier animals will help reduce the risk of loss or incidence of carriers of these diseases in flocks. A disadvantage is that these studies are useful if the patterns to be studied follow a recessive inheritance model, since only genomic regions fixed for a haplotype that is shared only among affected individuals can be identified; otherwise, the homozygosity mapping does not apply to dominant traits where symptomatic individuals may be homozygous or heterozygous in the causal mutation[76].

Through the information obtained by the GWAS it has also been possible to identify the modifications that domestic species have undergone and that are of interest from a morphological, behavioral, productive, adaptive, and, consequently, genetic point of view;

aspects that have allowed a better understanding of the processes involved in the evolution of their genome, as well as discovering and validating genomic regions involved in the manifestation of traits of economic and ecological interest[19].

Finally, genomics generates a large amount of information about the genetic composition of domestic animals; the complete genome of cattle, poultry, pigs, sheep, horses, fish, and other species of agricultural interest is currently available[9,10]. In recent years, the assembly of genomes has been improved in order to functionally annotate all the genetic information; once the functional annotation is completed, the new genomes would provide more efficient tools to study the genetic mechanisms that control the traits of interest of the animals and use or improve studies based on this information[42]. A different type of information generated by genomics are the SNP, which can be used simultaneously as population markers to verify affiliations, pedigree, and to perform phylogenetic studies[81].

Perspectives and challenges of sheep farming regarding the use of GWAS and genomic selection

The discovery and development of new markers for traits of interest, or that solve a problem in production systems, is conditioned by the availability or generation of phenotypic information (records), an aspect that does not differ from traditional selection. In Latin America, the use and availability of records is scarce; therefore, genetic progress is also scarce.

Several GWAS and genomic selection studies have found that creole animals are important biodiversity reservoirs, have resistance to diseases, high prolificity, good yield and productivity in difficult environments, traits that are genetically determined and that would be of great importance to introduce in other populations. Therefore, the sheep production chain in Latin America should consider the usefulness of zoogenetic resources since these animals constitute a future alternative to support commercial production.

A challenge for Latin American producers is to improve the traceability of products obtained from sheep farming. With the current molecular techniques, it is possible to establish traceability mechanisms in which by identifying the DNA of the products, these can be traced, which would contribute to revalue the traditional production systems.

Implementing conservation and breeding programs for local breeds in Latin America, which are generally maintained by small-scale producers, implies a great challenge. Recording behavioral data under these conditions is extremely difficult and, in some situations, impossible.

The cost-benefit relationship of the implementation of DNA tests to assist the genomic selection of traits of economic interest in sheep is related to the objectives of each production system. That is, the investment in this kind of tests is justified if the magnitude of the positive change provided by them generates economic profit through the expected results.

In Latin America, the use of these tools has been effective in commercial production, generally intensive with purebred or improved animals, where it is possible to obtain phenotypes that can validate the usefulness of genetic markers. In Latin America there is a wide variety of breeds, without considering those that have disappeared and that are important due to their adaptation to various ecosystems, determining factors in some regions. Therefore, the use of this type of study to detect genes or selection footprints that may be of importance for the conservation of these animals is very useful.

Conclusions

Although genomics is a helpful tool for understanding the architecture of complex traits of productive interest and improving sheep production systems, its use in Latin America is limited to a few countries; generally, those with the largest sheep population and a worldwide representative production. Therefore, it is relevant to continue researching the use of GWAS in Latin America and thus identifying more genes that influence the productivity of sheep, which are generally creole animals adapted to tropical conditions.

Acknowledgments

Conflicts of interest

The authors declare that they have no conflicts of interest regarding the work presented in this report.

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