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Review

# Genomic regions, genes, and single nucleotide polymorphisms in resistance to gastrointestinal nematodes in sheep. Review

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**Abstract:**

Several factors can modify productivity in sheep flocks; one of them is gastrointestinal (GI) parasitosis by nematodes, which can cause weight loss, growth retardation, and, in extreme situations, death. Parasite infections involve the immune system for resistance or susceptibility; therefore, strategies are currently being sought that will currently be efficient in the long term to reduce this affectation. One of these strategies is precision livestock breeding, which consists in the identification and selection of genetically resistant animals, using molecular markers. The objective of this review is to gather novel information on quantitative traits (IQT) and genome-wide association studies (GWAS), which confirm the relevance of certain regions or genes in resistance to ovine gastrointestinal parasitosis. Likewise, the potential relevance of new regions was analyzed to perform finer mappings

and find sets of polymorphisms that may allow a more efficient selection, while also considering the particular conditions of the sheep herds.

**Keywords**: Polymorphisms, Resistance, Gastrointestinal parasitosis, Sheep.

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# Introduction

One of the factors that can modify sheep productivity is gastrointestinal (GI) parasitosis; among its adverse effects are weight loss[1] growth retardation and, in extreme situations, death[1,2], aspects that directly affect the economy of sheep producers. Strategies are continually being developed to lessen the effects of infection, either by testing new drugs or by searching for animals that are genetically more resistant in order to reproduce them. Some authors mention that these strategies tend to be more efficient, in the long run, when they are based on multiple approaches[3,4].

Genetic variation between or within breeds allows the detection and genetic selection of individuals with a greater capacity to resist the consequences of helminth infections. Selection of sheep or goats for improved parasite resistance is considered a valuable option to complement other control measures[5]. The term disease resistance is commonly used generically to refer to resistance to infection or resistance to the consequences of disease, i.e. disease tolerance. Strictly speaking, however, disease resistance describes the host's ability to interact with and control the parasite's life cycle. Within the context of GI parasitosis, this may include the probability of establishment of ingested larvae, the rate and degree of parasite development within the host, mortality and fecundity of the parasites, and thus the fecal egg count. On the other hand, disease tolerance is used to describe the ability of the host to resist the pathogenic effects of infection[1].

Genetic improvement for resistance is possible due to the existence of a wide genetic variation in animals. When looking for genetic associations, traits of resistance or susceptibility (fecal egg count (FEC), parasite load, worm size and fecundity): immune response (major histocompatibility complex-MHC, concentration of antibodies such as IgA, IgG and IgM); impact of infection (anemia, presence of pepsinogen, or fructosamine concentrations), or resilience (growth rate and frequency of treatment required) are regularly

studied[3,6]. There are a number of important scientific contributions linking genes of the ovine major histocompatibility complex (Ovar-MHC) to the ability of sheep to resist infection by gastrointestinal parasites[7–16]; however, the effect of the MHC is reportedly small and accounts for approximately 11 % of the total phenotypic variation[7]. Class 1 genes are among the most polymorphic genes; this diversity, together with the lack of clarity of genomic organization, makes it difficult to identify new alleles of interest in sheep, which results in an evident scarcity of information[17]. The products of Class I and II genes are glycoproteins that present antigenic peptides to the T-cell receptor (TCR) of cytotoxic CD8+ and helper CD4+ lymphocytes, respectively[18,19]. Class II DRB genes have been more extensively studied[18,20] and have shown consistent associations with the phenotype of resistance to GI nematodes[7]. Current approaches may neglect this important molecule because statistical analyses to detect association between MHC alleles and disease depend partly on haplotype frequencies[21], whereas the ability to discriminate with causal point mutations depends on the degree of linkage disequilibrium (LD), as, when LD is high, alleles at different loci are often inherited together by the offspring, and the effects of the various loci cannot be easily disentangled[22]. Due to the high polymorphic variation in MHC, it is necessary to construct haplotype combinations to associate it with resistance/susceptibility traits[21,23], since most MHC genes are inherited in bloc as a haplotype with rare recombination events[24]. Use of MHC as a generalized marker requires deepening of knowledge to the point of sequencing already associated haplotypes and knowing in which race and for which parasite they can be validly utilized; the association of haplotypes may then become stronger than the allelic association with single nucleotide polymorphisms (SNPs).

New strategies such as the use of arrays or chips with thousands of polymorphisms for simultaneous genotyping may predict the genetic merit of an individual through clusters of single nucleotide polymorphisms[25]. Genotyping arrays have been developed by such companies as Illumina and Affymetrix, together with the Sheep Genomics Consortium, at different densities and with different coverage within the genome; currently the most commonly used in genome-wide association studies or determination of genetic merit are high and medium density, which can detect approximately 606,000 and 50,000 (50 K) evenly spaced SNPs. It has been observed that the estimated level of development for markers separated by less than 1Mb in arrays of up to 12 K can be a suitable tool to identify genomic regions associated with traits related to resistance to GI parasites[26]. In addition to this, there are intergenic regions, called "genetic deserts"[27], which are regions with non-coding sequences but also with unannotated regulatory elements that offer a promising potential for future research.

While resistance or susceptibility to gastrointestinal parasitosis may be controlled by multiple loci with small effects, epistasis relationships could be evaluated as part of the resistance architecture. In addition, epistatic relationships allow the regulation of the expression of

neighboring genes, which in turn make the expression of other genes possible. To date, no studies have identified major genes as the only genes involved in resistance in gastrointestinal parasitic infections. Therefore, the objective of this review is to present genomic information that confirms the relevance of certain regions or genes, and to give new relevance to others in GI parasitosis by nematodes in sheep.

## Recent findings of genes or genomic regions involved in resistance/susceptibility to gastrointestinal nematodes

Nematodes can be located in different regions of the gastrointestinal tract; for example, in the abomasum the most frequent are *Haemonchus contortus*, *Trichostrongylus axei*, *Mecistocirrus digitatus*, and *Telodorsagia circumcincta*, while *Trichostrongylus colubriformis*, *Cooperia* spp., and *Nematodirus* spp. are prevalent in the small intestine, and *Oesophagostumum* spp., *Chabertia ovina,* and *Trichuris ovis*[28–30] predominate in the large intestine. In general, it can be said that the nematode usually found worldwide, especially in tropical and subtropical regions or climates, is *H. contortus*[31], whereas *Telodorsagia circumcincta* is one of the most prevalent in cold regions[32]. It has been hypothesized that the inherent GI resistance to parasites is given by several genes (polygenic), and that it is related to the immune system[33–35].

Four main mechanisms can be identified that determine the host's response to GI parasite infection: 1) the mechanism of the innate immune response, 2) protection of gastric mucous membranes, 3) hemostasis pathways, and 4) acquired immunity[36]. On the other hand, among the mechanisms that allow the expulsion of parasites are the following: hypermotility, gastric hypersecretion and goblet cell hyperplasia with subsequent increased mucus production. *In vitro* and *in vivo* studies have shown that the immediate expulsion of parasites is associated with the presence of histamine and leukotrienes in the mucus of the abomasum that inhibit parasite motility[37,38]. High concentrations of histamine in the abomasal mucosa of hemoncosis-resistant sheep may allow parasite expulsion, promoting abomasal hypersecretion that decreases worm fecundity and motility[39,40].

With respect to the host immune response, it has been observed that there is a clear difference in the immune response of lambs that have been challenged once or twice in their lives, and adult ewes that have been challenged several times during their productive lives with different larval or worm stages[31,37,40]. Lambs demonstrate competent immunity by the age of 2 to 3 mo[41], and if larval exposure challenge is constant, immunity develops with a significant protective response by the age of 10 to 12 mo[42,43]. In adult sheep this immunity tends to remain, rendering them relatively resistant to infection, and low-level exposures

make them retain immunity[44]. In some studies, protection against GI parasitosis has been associated with the Th2 helper immune response[45,46], characterized by the production of interleukin (IL) 4 which is an important cytokine in the immune control of parasitic GI diseases[47,48], essential in the maturation of virgin CD4+ T cells through the STAT6 pathway[49,50]; it also promotes the differentiation of high synthesis rate B cells (changing the heavy chain from IgM to IgE and IgA)[51–53], as well as the recruitment of eosinophils, basophils and mast cells to control infection and participate in the expulsion of helminths[54–56]. IL-13 acts in concert with IL-4 to stimulate IgE class switching, promote healing by tissue fibrosis, and enhance larval expulsion by increasing mucosal permeability, mucus production and muscle contraction[57–59]; IL-5 too stimulates eosinophil maturation. The positive upregulation of these two cytokines after infection with *T. columbriformis*[58,60], coincides with the increase in IgE and IgA production[61]. The development of the Th1 cellular response prevents the expression of proinflammatory cytokines such as interferon gamma (IFN-γ), and, therefore, the Th2 response[55,62]. There is a link between IFN-γ and susceptibility, as it negatively regulates IL-4 and, consequently, the differentiation towards the Th2 response[63,64].

During parasite infection, the concentration of IgA is more important in the abomasum than in serum, and a negative correlation has been observed between the amount of specific IgA in abomasal mucus and the parasite load in infections by *H. contortus*[65]. This situation has also been evident with the nematode *T. circumcinta* found in sheep abomasum, where high levels of specific IgA in the abomasal mucus have decreased the fertility and length of the nematode[66]. A typical feature of helminth infections is the production of specific IgE as a result of a Th2-type response. IgE is able to induce antibody-dependent cytotoxicity of eosinophils, mast cells and macrophages. Increased local IgE levels have been associated with resistance to GI parasitosis in sheep and goats[67–69].

There are reports of resistance/susceptibility in such breeds as Churra, Red Maasai, Merino[70], Dorper x Red Maasai crosses[71], Scottish Blackface[72], St. Agnes[26], Soay feral sheep, Djallonké[73], Border Leicester x Merino, Poll Dorset x Suffolk or white Dorper crosses, Kathadin[74], Tunisian Native sheep[75], Corriedale, Pampinta[76], Sardas[77], and Florida Native sheep among others[78]. In addition, other studies in hair breeds such as the Red Maasai[79], Florida, Santa Cruz, Barbados Black Belly, and Navajo[80] have shown that they are more resistant to nematode infection and its consequences than European breeds. However, there is variation between hair breeds, as shown in a study comparing Pelibuey versus Kathadin lambs; Pelibuey lambs showed greater resistance to natural GI nematode infection compared to Kathadin lambs, sharing the same climatic and grazing conditions, associated with the phenotype of egg counts per gram of feces and peripheral eosinophil counts[81].

Traditionally the association is made with such traits as fecal egg count, because it is a direct manifestation of the host's inability to control parasite reproduction[37,82]. Another is the FAMACHA index, which is an indirect measure of the presence of parasites in the abomasum and the severity of the anemia they can cause to the host, and is related to the reduction of the agglomerated cell volume (measured in percentage), sequelae of infection with parasites such as *H. contortus*, which highlights the host's inability to replenish red blood cell levels and, in an extreme situation, could lead to death; but if the individual tolerates the acute infection and does not die, maintaining its zootechnical activity may be a resilience trait[76]. Animals infected with *H. contortus* show more severe anemias[82,83]. In initial studies, these traits have been associated with regions on chromosome 20 (OAR20; OARn = *Ovis aries* chromosome number "n"), which contain MHC II alleles, and OAR3 on the gamma interferon gene (IFN-ɣ) or genes close to this region[84–86]. Another systematic review, mentions that there is sufficient evidence regarding the association of the IFN-ɣ gene and resistance to *T. circumcincta*, and it has been suggested that this region and its neighboring genes are of interest in host resistance[36,84–88].

Other studies in which no association has been found with the abovementioned regions, point to this difference as being attributable to the characteristics of the study subjects, as associations have been found only in lambs, not in adult sheep[87,89].

Other data provided for Red Maasai x Dorper sheep suggest that variation in SNP markers located in immune cell signaling genes such as suppressor of cytokine signaling (SOCS2), ubiquitin E2-conjugating enzyme (UBE2N) and protein tyrosine kinase substrate 15 (EPS15), could favor Th2 cytokine production to enhance the biological function of eosinophilia, mastocytosis and humoral response (high IgE levels) at the site of infection. Mucus production by the action of genes such as MUC15 or GALANT4 and hemostasis pathways (ATP2B1) may be important mechanisms contributing to the phenotype or in the differences in parasite resistance in the Red Maasai x Dorper population[72], and describes two regions that had not been associated until then: OAR2 (162-163Mpb) and OAR3 (44Mpb). The data also show that the OAR6_81718546 polymorphism (close to the platelet-derived growth factor receptor-α PDGFRA) is associated with effects on the aggregate cell volume, as has been previously reported in sheep of the Brazilian Morada Nova, Spanish Churra [34], and Soay Feral breeds[78] and in the Red Maasai x Dorper cross. Markers affecting fecal egg count (OAR5_111342555, OAR15_35337227, OAR5_100699982.1, DU183841_402.1, OAR15_40719719.1, OAR15_40926306.1, OAR7_4206430, and OAR17_42673146) do not affect agglomerated cell volume or live weight according to this study[72].

On the other hand, twelve SNP's listed in Table 1 were analyzed in the Soay Feral breed, of which, RORC2 p.A404T (100,653,186 bp) is associated with IgA; in addition it was concluded that the IL23R p.V32M polymorphism (42,512,431 bp) is related to the IL-23

receptor, an inflammatory cytokine that exhibited association with body weight at 20 days in blackface lambs[78].

In 2016, associated genes were found in Spanish Churra breed for the fecal egg count trait in OAR6 (with peak at 88. 1 cM) as AFP, ALB, AMBN, AMTN, AREG, BTC, CXCL1, CXCL10, CXCL11, CXCL9, EREG, GC, IGJ, IL8, MUC7, PF4, PPBP, RASSF6, SCARB2, TMPRSS11D; in OAR8 (peak at 2 cM) for the same trait, as CD109, COL12A1, MYO6, and in OAR 22 (peak at 3.4 cM), for the IgA trait of gene PCDH15. Among the nematode species found most frequently in this study were *Trichostrongylus* spp. and *Teladorsagia* spp. In addition, other genes encoding for chemokines were found, including IL-8, CXCL1, CXCL10, CXCL11, CXCL9, PF4, PPBP —molecules that are of great importance in the immune system, since they are involved from leukocyte recruitment to cell communication and activation during infection; particularly IL-8, CXCL8, and CXCL1 are involved in the recruitment and activation of neutrophils. Notably, this author found no clear correspondence with previously described classical regions related to IFN-ɣ or those involving MHC class II genes[34].

On the other hand, when evaluating Santa Inés sheep using a SNP chip with 12 785 single nucleotide polymorphic markers, an association was found between regions in OAR1, OAR2, OAR3, OAR5, OAR8, and OAR15[78] (Table 1). Several candidate chromosomal regions described by the authors are related to the development of the immune system, its activation, inflammatory response, lymphocyte regulation, and leukocyte proliferation (B2M, SFXN1, IL25, BMP4, TSHR, CCL28, PIK3R1, FGF10, IL15, TP-1, BPMG, BCL10, HSPD1, MALT1), highlighting genes such as CD109, which is a surface antigen expressed by CD34 or IL-25 cells; coincidentally some of these were reported by another study[34] as potential genes in resistance to GI nematodes in sheep.

As of 2018, GWAS studies with high or medium density chips have elucidated more candidate genes that could be relevant in resistance/susceptibility to nematodes and other parasites. This is indicated by the findings of several authors[75,77,90], one of them in Djallonké lambs from West Africa, where five genes (TRIB3, CDK4, CSNK2A1, MARK1, and SPATA5) are associated with resistance traits related to immunity and cell proliferation. It is also suggested that the MBL2 gene (as the basis of a QTL) in OAR22 is related to IgA levels[27,82]. Also, it has been hypothesized that genes involved in lamb growth and size (such as the ADAMTS17 gene in OAR18) may be pleiotropic with certain genes that determine resistance traits to GI parasite infection; however, the association between these genes has not yet been clearly determined[34,73,91].

OAR2 is also highlighted in a study in Australian sheep of breeds such as Merino or Border Leicester x Merino, Poll Dorset/Suffolk/Suffolk/White Suffolk/White Dorper/Border Leicester crosses, where, in a first analysis, the authors provide an outline of three SNP's in

OAR2 with a strong association to the trait of fecal egg count (rs421630816, rs424521894, rs413835864): the SNP rs421630816 (position in OAR2: 110.8 Mbp) in the PALLD gene, while rs424521894 and rs413835864 (position in OAR2:107.3 and 107.4 Mbp, respectively) in the GALNTL6 gene related to the synthesis of mucin-like glycans, which influence host-pathogen interaction. Likewise, these authors point out a region in OAR6 that includes six SNP's, where rs416517011 stands out for its level of significance in the association; they also found other associated genes in OAR18 and OAR24, hypothesizing that these genes share certain mechanisms with the immune system, suggesting potential interaction effects between genes[70]. Another contribution found significant associations in OAR2, 3, 16, 23, and 24 in Kathadin sheep[74]. A relevant finding is a locus located in OAR3, close to the C3 complement pathway receptor 1 gene (C3AR1). C3AR1 has been reported to be differentially expressed in susceptible versus resistant sheep[92] and has been associated with the Th1 response[93], also located in OAR16, 87 kb towards 5' of the *ITGA2* gene (α-2 integrin) that mediates adhesion of platelets and other cell types to the extracellular matrix. One region that stands out in OAR2 —the DIS3L2 gene (rs406850490 and rs422243920), an exoribonuclease involved in regulating the relative expression of Toll receptor type 4— was significantly associated and suggests a potential role in mediating resistance. The DIS3L2-associated SNP had a minor allele frequency (MAF) overrepresented in resistant sheep (0.479) compared to susceptible sheep (0.094); this exoribonuclease may affect IL-10 expression by repression of let-7, a miRNA. Other findings of importance in the study refer to OAR3 ALK-tyrosine kinase receptor (rs437558829 and rs407346502) and C3AR1, OAR19 (rs406978752) GRM7-(metabotropic glutamate receptor 7), OAR23 (rs399876637) SLC14A2 (urea transporter 2) and OAR24 ZP3 glycoprotein (rs423186265); however, it has been suggest that these findings need to be validated[74].

In order to give prominence to the effects of the immune system on the response to parasitosis, another group studied indigenous Tunisian sheep under traditional grazing management and they highlighted RUFy4 and VIL1, two IL-8 receptors (CXCR1 and CXCR2) as candidate genes involved in the immune response in the GI tract, hypothesizing that they may be involved in repairing damaged tissue in the intestine and enhancing neutrophil recruitment and inflammation. They also found two cation transporter genes such as SLC22A4 (OCTN1) and SLC22A5 (OCTN2) involved in the transport of oxourea. The authors stress that the traditional management of these sheep allows them to develop multiple adaptive strategies that make them resistant to parasitosis, and the information gathered from this type of native livestock is very valuable in understanding the architecture of resistance[75]. In Mexico there are herds with Creole characteristics and extensive management; therefore, it would be interesting to determine if the adaptive strategies of the immune system coincide with those of other herds, or other breeds, managed under similar conditions, and thus be able to identify coinciding mechanisms for use as markers for resistance/susceptibility to nematodes or other parasitosis.

Notably, a fine mapping carried out by Argentine researchers in Pampinta and Corriedale lambs under natural challenge found that certain regions that had been previously associated[36], in OAR3 and OAR6, and OAR20, contain genes involved in MHC-mediated antigen processing and lymphocyte signaling pathways. The OLA-DRA1_479 SNP was the only SNP that showed a significant association for the traits under study in Corriedale lambs; it also associated polymorphism of C-type lectin receptors that mediate functions such as cell signaling transduction processes, pathogen recognition, and innate immunity, although CLEC12A acts by inhibiting the production of IL-12, TLR4-dependent TLR4 and IL-12[94]. It also marked three significant *de novo* SNP´s, FOS_109, IL20RA_422 and TIMP3_716 —the first, located in FBJ murine viral osteosarcoma homologous gene; the next, in IL-20 receptor gene, and the last, located in TIMP a metalloproteinase inhibitor in OAR 3, 7 and 8, respectively—; FOS_109 belongs to a group of proteins that regulate cell proliferation, differentiation and transformation. The duplicated expression of this gene in abomasal tissue was found to be associated with resistance in Merino sheep and it is hypothesized to be a relevant gene in primary infections by *H. contortus*. In some cases, FOS gene expression has also been associated with cell death by apoptosis. TIMP3_716 showed evidence that suggests association when using fecal egg count as a breeding value estimated as an association phenotype, and may be involved in the remodeling of damaged tissue in response to parasitic infections. The results obtained confirm genomic regions previously reported to be associated with nematode resistance in other sheep breeds, both for innate immunity (MASP, CLR, NLR, TLR, IL20R, FOS, TIMP) and adaptive immunity (CLR, IL2, OLA-DRA, TIMP) reinforcing the role of the host immune response against parasites[76].

In Sarda ewes and crosses of this line with Lacune, 10 regions with significant association to the trait of fecal egg count were mapped, pointing to 3,538 polymorphisms causing high-impact effects that can generate termination codons (nonsense mutations) in genes coding for 530 proteins. The authors of this study hypothesize that QTLs located in OAR 1, 12, 19, and 20 are strongly implicated in a complex mechanism of resistance in sheep to GI parasitosis; some of the polymorphisms they report can be seen in Table 1(77). In OAR12, the missense mutation c.103G>A in exon 2, position 39, 567,687 bp, in the TNFRSF1B gene (member of the TNF1B receptor superfamily), which is also close to the *SELE* gene (selectin E gene, four relevant nonsense mutations), encodes a protein in endothelial cells and is responsible for the accumulation of leukocytes at sites of inflammation mediated by vascular lining cells. Another authors[95] mentions that the *SELE* gene is negatively expressed in abomasal lymph nodes of lambs recently infected with *T. circumcincta*, suggesting it as a component of the resistance response to infection in GI parasitosis. In OAR19 the most significant association was in the MGR gene (metabotropic glutamate receptor, associated with nervous mechanisms in humans), in addition to 13 nonsense variants in the IL5RA gene (α-subunit of rIL-5). This protein has been found to be expressed in animals resistant to *T. circumcincta* (Scottish blackface lambs, churras ewes, and merino lambs)[95–97]. In the OAR20 region, a large region encompassing MHC class II was found, although these are reportedly located at

a distance of 4 to 6 Mb from the most significant location, highlighting that, due to the polymorphic nature of the gene, it is difficult to identify causal mutations or SNP's that are useful in resistance selection[98]. Also reported were mutations in IL17A, IL17F, TRIM26, TRIM38, TNFRSF21, LOC1011118999, VEGFA and TNF. A significant SNP (rs404860664) was reported in the LOC101111058 gene (butyrophilin-like protein); however, butyrophilin-like proteins suggest that it plays a role in the regulation of local intestinal inflammation in other species[99], with nine mutations in TRIM 26; these proteins play roles in the regulation of pathogenesis in autoimmune diseases and pathogen defense in particular against viruses[100], and they also may be involved in the down-regulation of several immune response genes[77].

In a first study detecting repeat variants by GWAS in native sheep in Florida, 8124 copy number variations (CNV) were identified, although only 14 were significantly associated with the traits under study, such as fecal egg count and aggregate cell volume. The genes that stand out in this study in relation to the immune response are CCL1, CCL2, CCL8, CCL11, NOS2, TNF, CSF3, and STAT34, which may play an important role in the resistance to *H. contortus*. These genes could be used as potential markers of resistance in this breed; it is also possible that genes close to repeat regions such as LOC101110424, DOCK9, ITGBL1, BIVM, TNFSF13B, ING1, F7, F10, PCID2, and GAS6 may have important effects on the immune response against the parasite[90]. For example, ITGBL1 gene expression is associated with immune cell infiltration[101], while genes F7 and F10 play a relevant role in the initiation of coagulation and defense against pathogens[102]. The CCL1 gene is part of an eotaxin chemokine and promotes the migration of activated eosinophils[103], eosinophilia is a common event in sheep infected with *H. contortus*[104], and this gene is commonly used as a marker of resistance[92,105]. In addition, three galectin genes (LOC101117947, LOC101118202 and LOC101102156) near a repeat region were associated with the egg count trait at day 28. Galectins are proteins involved in the immune response to parasitic infections of the gastrointestinal tract in sheep and are upregulated during infection with *H. contortus*[106]. Some of these galectins, like No. 11, can regulate larval growth and development by binding to *H. contortus* larvae No. 4 and adults[107]. The associated repeats for the cell package at day 0 and 28 (LOC101108321) are contained in genes related to multidrug resistance proteins (MRP), expressed at the same level in CD3+/CD4+ T cells according to a study performed in the peripheral blood of normal and refractory lymphoma patients[108]; they can also regulate the inflammation of intestinal mucous epithelia[109]. There is a possibility that all the repeated sequences found in this study may be segregated among the population, but as in other studies, they must be validated in other populations. These findings may contribute to the development of new strategies to improve parasite resistance in sheep and promote selective breeding through marker-assisted selection[90].

# Conclusions

Parasitosis and parasitic resistance are an issue that affects sheep production systems, especially grazing sheep. Knowledge about the architecture of resistance/susceptibility in sheep contributes to genetic improvement at a faster rate, resulting in higher productivity in flocks that contribute to precision livestock breeding. Although effective drug treatments to fight parasitosis can be found in parallel, when new formulations become available, they can potentially be more expensive. There is also a growing interest in reducing the use of anthelmintics to contribute to the environment by reducing their excretion into the environment. The information from QTLs has been refined by GWAS analysis with high-density chips, creating the need for further fine mapping of candidate genes, so that the information may be utilized to screen sheep for resistance to GI parasites or to elucidate epistatic relationships between immune response genes in order to generate areas of research for functional or expression studies, providing greater clarity on the function of the immune system. Dissection of the architecture of resistance and susceptibility to gastrointestinal parasitosis, as well as the validation of associated loci in different herds, create the challenge of generating a marker test with the best possible combination of SNPs to allow characterizing individuals resistant to GI parasitosis among certain populations as a strategy to address parasitic resistance and implement more effective and direct selection programs.

**Table 1:** Findings of genomic regions, SNP's and genes linked to association variables in resistance to gastrointestinal parasitosis in sheep

| **Author** | **Parasite** | **Association variables or traits** | **QTL** | **SNP** | **Genes** |
|---|---|---|---|---|---|
| Benavides, 2015 | *Haemonchus contortus* | AVCA*, LW** | OAR2 (15 Mbp), OAR11 (58 Mbp) OAR15 (54 Mbp). New OAR2 (162-163Mpb) and OAR3 (44Mpb). | OAR6_81718546, OAR5_111342555, OAR15_35337227, OAR5_100699982.1 DU183841_402.1, y OAR15_40719719.1 OAR15_40926306.1 OAR7_4206430 y OAR17_42673146, | *SOCS2, UBE2N y EPS15 ATP2B1 y LRP8 MUC15 y GALNT4* |
| Atlija, 2016 | *Trichostrongylus* spp *y Teladorsagia* spp | | OAR6 (peak in 88.1 cM), OAR8 (peak in 2cM) y OAR22 (peak in o 3.4 cM) | | *AFP, ALB, AMBN, AMTN, AREG, BTC, CXCL1, CXCL10, CXCL11, CXCL9, EREG, GC, IGJ, IL8, MUC7, PF4, PPBP, RASSF6, SCARB2, TMPRSS11D, CD109, COL12A1, MYO6 PCDH15, IL8, CXCL1, CXCL10, CXCL11, CXCL9, PF4, PPBP, CxCL8 y CXCL1* |
| Berton, 2017 | *Haemonchus contortus* | FEC***, FAMACHA index, AVCA | OAR 2:91681809-9470993 2:140765269-143337545 OAR 3:195904655-195904655 | | *LPAR1; TXN; ALDOB; PLPPR1; CTSV; PTCH1; AGTPBP1; AQP3; ADRA1A; LOXL2; SFTPC; HR; LPL; LOC101123612; TGFBR1; GNA14; PCSK5; RORB; ALDH1A1; TYRP1; FREM1; PSIP1; CCDC171; BNC2; CNTLN; ADAMTSL1; RPS6; TP-1 XIRP2; LOC101109253; SCN7A; SCN9A; SCN1A; TTC21B; GALNT3; CSRNP3; LOC101110039; SCN2A;* |

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| | | | OAR 1:56799547-56799547<br><br>OAR 16 :41876371-41876371<br>OAR 18:68738392-68738392 | | *SCN3A, DHX57; GEMIN6; RSF7; GALM; HNRNPLL; LOC101119897; LOC101120157; ATL2; LOC101120655; LOC101120913; LOC101119706; RMDN2; CDC42EP3; TRNAC-GCA; TRNAS-GGA; QPCT; PRKD3; NDUFAF7; CEBPZ; SULT6B1; EIF2AK2; GPATCH11; HEATR5B; STRN; VIT; FEZ2; LOC101122183; LOC101122430; LOC101122685; LOC101123283*<br>*GALNT2; TRNAE-UUC; PGBD5; LOC101103868; LOC101104120; LOC101104369; LOC101104630; LOC101104883; LOC101105131; LOC101105384; LOC101105628; LOC101105878; LOC101106137; LOC101106392; LOC101106652; LOC101106903; LOC101107159; LOC101107409; LOC101107663; LOC101107927; LOC101108188; LOC101108450; LOC101108625; LOC101108717; LOC101108881; LOC101109143; LOC101108983; LOC101109240; LOC101109508; LOC101109767*<br>*PDZD2; LOC101119673; C16H5orf22; DROSHA; CDH6*<br>*INF2; ADSSL1; SIVA1; AKT1; TMEM179; PLD4; LOC101104938; C18H14orf79; LOC101105444; GPR132; LOC101105953; BTBD6;* |

| | | | | | |
|---|---|---|---|---|---|
| | | | | | *BRF1; LOC101106466; LOC101106718; C18H14orf80; TMEM121; LOC101107475; LOC101107738; LOC101107998; LOC101108260; LOC101108522; LOC101108781* |
| Wilkie, 2017 | ****NE | FEC, IgA, LW | | RORC2 c*25T>C and RORC2 c.*109[a]>g E294Q y A404T) IL23R p.V324M y RORC2 p. A404T | *TBX21, RORC2 e IL23R* |
| Álvarez, 2019 | NE | AVCA, $FEC_{log}$, AVCA, FAMACHA | | OAR1_55820164.1 OAR2_117867801.1 OAR8_16568165.1 OAR15_88875909.1 OAR18_43101149.1 OAR2_140684314.1 S16493.1 (OAR16) S43307.1 (OAR7) OAR8_8982479.1 OAR15_2525103.1 OAR17_3451123_X.1 S43852.1 (OAR19) OAR2_64824262.1 OAR3_77774489.1 OAR3_161498140.1 OAR12_22189408.1 S32476.1 S09612.1 (OAR13) OAR18_5508052_X.1 OAR22_6293170.1 OARX_107840506.1 | *TMOD1; TDRD7, MFSD6, INPPI, HIBCH, C2H2orf88, SV2C, IQGAP2, NUDT6 TRIB3, CDK4, CSNK2A1, MARK1 y SPATA5, MBL2, ATP6V1E2, TMEM247, EPAS1, ATP23, CTDSP2, AVIL, TSFM, METTL21B, METTL1, LOC101116039, MARCH9, CDK4, TSPAN31, MARK1* |

| | | | | | |
|---|---|---|---|---|---|
| Kaladeh, 2019 | *H. contotus, T. colubriformis, T. circumcincta* | FEC | | rs421630816, rs424521894, rs413835864, rs421630816, rs424521894 y rs413835864, rs413835864, rs424521894 y rs421630816, rs416517011 | *PALLD, GALNTL6* |
| Becker, 2020 | *Haemonchus contorutus* | Estimated genetic values and FEC, and FAMACHA index | | rs406850490 y rs422243920, rs437558829 y rs407346502, (rs406978752, rs399876637, rs423186265 | *C3AR1, DIS3L2* |
| Ahbara, 2021 | NS | | QTL FECGEN | | *SLC22A4, SLC22A5, IL-4, IL-13, IL-4, VIL1, CXCR1, CXCR2, IL-4, IL-13, FECGEN, TFEC_1, HFEC, NFEC, LATRICH_2, IGA, OSAS, WORMCT, PEPSL y CEOSIN QTL, RUFy4 y VIL1, ITLN* |

* AVCA= average volume of the cell agglomerate; ** LW= live weight; *** FEC= fecal egg count; ****NS= not specified.

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The authors declare that they have no conflict of interest.

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