

An In-Depth Review of Sheep's Genetic Immunity to Gastrointestinal Parasitic Nematodes

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Abstract

Sheep farms have a significant challenge due to gastrointestinal nematode infections, which can lead to higher management along with treatment expenses, decreased output and even death in extreme situations. The hereditary resistance of sheep against gastrointestinal parasite nematodes is described as certain genes that modulate the immune system, diminishing vulnerability to infections and fostering resistance among the populace. An overview of the current state of knowledge about sheep gastrointestinal nematode infectionresistant indicators and the host immune response is presented in this paper. It has been shown that some sheep breeds and people are more resistant to gastrointestinal nematodes due to genetic polymorphisms. Breeding strategies aimed at improving host tolerance to illnesses might contribute to a lasting reduction in the issues. Attempts have been undertaken to distinguish between vulnerable and resistant animals based on indicator features. Genes with a recognized biological role that either directly or indirectly control how the illness under investigation develops are known as candidate genes. It has been demonstrated that the genes are linked to disease and they are more likely to be associated with the specific features of the disease. By identifying the genetic markers, breeding programs are able to apply marker aided selection, which improves selection accuracy. This review summarizes the key points on relevant genomic regions for GIN resistance or vulnerability phenotyping, the relationship between resistance markers and economically important production characteristics in sheep and various parameters used to assess nematode resistance.

Keywords: Candidate genes, gastrointestinal nematode, genetic markers, sheep, host resistance

INTRODUCTION

The most common parasites in the world that affect sheep are Gastrointestinal nematodes (GINs), which have a major financial impact on the sector due to their impacts on animal productivity and treatment costs. Teladorsagia circumcincta, Trichostrongylus colubriformis and Nematodirusbattus are the three most significant GIN species of sheep in temperate regions, but Haemonchuscontortus, which feeds on blood, is more common in tropical locations (1). Increased pasture contamination results from GIN's high agglomeration among the host population, which allows vulnerable individuals to harbor thousands of worms. The rising prevalence of anthelmintic resistance poses a challenge to the current sheep production methods, which rely on the supply of effective anthelmintic products. The prospect of widespread anthelmintic resistance has sparked a fresh focus on immunomodulatory anthelmintics, breeding for resistance and immunization as alternate worm control methods (2). The most popular technique for identifying hosts with a resistant phenotype is fecal egg count along with FEC are two reliable biological markers that can be used to determine whether sheep populations are resistant and vulnerable. Nonetheless, a number of variables can restrict FEC, such as the host immune system state, diet composition, breed of sheep and variations in GIN species fecundity (3). Grazing animal parasite infections are one of the primary causes of productivity losses in small ruminants globally. Helminth infections, for example, cost the European sheep farming industries € 151 million annually for dairy sheep and € 206 million annually for meat sheep. Our findings demonstrated that sheep with parasite infections suffered a significant economic loss (4). The parasite reduces an animal's productivity, weight and conception rate, changes the makeup of the



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carcass and has clinical consequences such as coat roughness, edema and diarrhea that result in significant losses for farmers. The management of gastrointestinal nematodes needs an integrated approach that blends chemical and nonchemical methods. The integrated control approach includes management techniques that reduce infection, genetic selection for host lines coupled with breeds to enhance host resistance, endurance to parasites, targeted deworming of infected and particularly vulnerable individuals. The management of pastures, together with timely diagnosis and planned prevention, helps to control gastrointestinal nematode infection (5), as shown in figure (1).



Figure (1). Roundworm Life Cycle (Source: <u>https://www.zoetis.com.au/livestock-solutions/images/sheep-</u> effective-parasite-management/sheep_drench_flow.jpg)

The paper (6) designed a gastrointestinal nematode (GIN) that naturally exposed the sheep with high or low parasite loads for controlling sheep's GIN to identify important genes for regulation and biological mechanisms connected to GIN infection. The paper (7) estimated the genetic characteristics of novel and prevalent illness phenotypes in Scottish Blackface sheep that are linked to coccidian and natural nematode infection. The information obtained is useful in supporting future tactics for genetically improving parasite management. The paper (8) used a network analysis to find possible biomarkers linked to ovine GIN resistance. Data mining from literature was used to reconstruct comprehensive gene and protein interaction networks for potential genes engaged in the most relevant immunological pathways linked with resistance to ovine GINs. The paper (9) compared the classification performance of various approaches, evaluated farm appropriateness for the optimal categorization model and examined the viability of forecasting sheep that are vulnerable, robust and resistant to gastrointestinal nematodes based on easily assessed phenotypic features. The paper (10) discussed in the literature regarding the various parameters are considered to assess sheep resistance status to nematodes, primarily Haemonchuscontortus, the relationship between resistance markers and key production traits that are economically significant and the major genomic regions found to be significant in determining the phenotype for GIN susceptibility or resistance. The paper (11) examined the impact of copy number variants (CNVs) on immunity to spontaneously occurring Haemonchuscontortus infections. The paper (12) examined 600 K genotypes of single nucleotide polymorphisms in naturally managed autochthonous Tunisian sheep that were grazing community natural pastures, both infected and non-infected with GIN. Genetic differences related to the presence or absence of infection weren't identified by population structure analysis. The paper (13) investigated if sheep with Haemonchuscontortus infection's feed consumption and feed efficiency would be affected by genetic selection aimed for GIN confrontation. The paper (14) determined how effective it was to incorporate genomic data into the studies, Santa Ines sheep were evaluated for resistance to gastrointestinal nematode infection (RGNI) and body size using several relationship matrices. The paper (15) used a whole genome scan to examine how genetic variables, both additive and non-additive, affect Florida native sheep's ability to fend against spontaneous Haemonchuscontortus illnesses.

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A significant hindrance to the sheep business, intestinal nematode infections result in decreased productivity, higher management and treatment expenses and in extreme cases, even death. Because of their close grazing habits, sheep are sometimes referred as a museum of parasites. Sheep output is limited by parasites called gastrointestinal nematode infections, which include Oesophagostomum sp., Bunostomum sp. and Haemonchuscontortus. Grazing ruminants are subject to gastrointestinal nematodes as a persistent natural threat. Clinical illness and productivity losses result from infection with these parasites. One main factor contributing to sheep morbidity and death is intestinal nematodes. In India, using anthelmintics is the method for controlling gastrointestinal nematodes. However, anthelmintic-only management is vulnerable because of residues in cattle products and the pervasiveness of anthelmintic resistance. Numerous accounts exist of parasites developing resistance to the majority of anthelmintic classes that are on the market. New control methods are required in addition to anthelmintics that are resistant to use in animal products due to residues in those products, customer demand for organic goods and negative environmental effects (16), as shown in figure (2).



Figure (2). Haemonchus contortus life cycle in sheep (Source: https://www.mdpi.com/2076-2615/12/18/2339)

Host resistance to intestinal Nematodes infection varies genetically

Certain sheep breeds and individuals have been shown to be more susceptible to gastrointestinal infection caused by nematodes' genetic differences within and between breeds. Based on indicator features coupled with other factors, vulnerable and resistant animals were distinguished in efforts. Numerous investigations have documented the genetic underpinnings of sheep variances between and across breeds, along with immunity to gastrointestinal nematodes. Breeds of sheep have been shown to differ in their resistance to gastrointestinal nematodes. Using molecular genetics, determined the variation present in Suffolk and Texel sheep at the ovine MHC-DRB1 locus. The Ovar-DRB1 gene is crucial for the Suffolk breed's resistance to nematode infection, based on studies on fecal egg count in Texel and Suffolk lambs and Ovar-DRB1 alleles (17).

A few researches on the vulnerability of breeds to nematode parasitism have been conducted in India. The author reported that following artificial infection with H. contortus, Hisardale lambs (Nali x Corriedale) had reduced body weight growth, hemoglobin and packed cell volume; whereas Munjal lambs (Nali x Lohi) had greater peripheral eosinophil count. They came to the conclusion that Hisardale lambs are more vulnerable than Munjal lambs to experimental H. contortus infection. Lambs from Malpura had the smallest FEC and following Avikalin, while Bharat Merino lambs had the highest FEC, according to the author, researchers observed variations in vulnerability between sheep breeds in the FEC of naturally occurring *H. contortus* infection. Two divergent lines were produced by selecting progenies from sires with low and high mean FEC. The progenies of



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the Avikalin (Rambouillet \times Malpura) breed were examined by the author for FEC at the native and exposed stages of natural infection.

There is genetic heterogeneity for natural and learned immunity against illness, as seen by estimations of the heritability of FEC during the exposed and native phases of infection by nature, which were 0.240 ± 0.185 and 0.120 ± 0.115 , respectively. The findings show that opposition to *H. contortus* is inherited and the possibility of obstacle selection, along with that selection for resistance, lacks a negative impact on semi-arid environment production metrics.

The *Garole* breed exhibited a noteworthy increase in internal nematode resistance in comparison to the *Deccani* and *Bannur* breeds, as reported by the author. In Indian Avikalin sheep, the number of fecal eggs was determined using genetic characteristics was calculated. The characteristic has 0.149 ± 0.096 direct heritability. The study found a substantial correlation between the number of fecal eggs and growth features (18). Additionally, the results indicated that the trait was influenced by maternal permanent environmental impacts and direct genetic influences. Therefore, strategies to enhance the trait should take both factors into account.

Variations in Genetics within a Breed

To generate sheep resistant to *H. contortus*, genetic diversity among breeds has been utilized. Merino flocks that were effectively chosen for their strong and low immunological responses to T. colubriformis and H. contortus and Romney sheep that have been shown to be independently selected for nematode confrontation have demonstrated this ability. In sheep, the heritability of infection resistance ranged from 0.22 to 0.43, as determined by FEC. Once Merino ewes were artificially challenged with H. contortus of FEC, the author observed estimated heritability's of 0.27, 0.22 and 0.31. The heritability of FEC in Merino sheep was determined to be 0.42 by the author following a naturally acquired Ostertagia infection. In a different investigation, the author found that Romney sheep with a naturally acquired mixed species infection with FEC had an estimated heritability of 0.34. A number of researchers the author reported on the heritable differences in FEC. After that is tested for PCV and FEC, Merino sheep and lambs were inspected for resistance to spontaneous infections caused by *H. contortus*. The findings demonstrated that the FEC might be applied to select sheep that are resistant to infection by *H. contortus*.

Resistance to *T. colubriformis* and *H. contortus* has been linked genetically in INRA 410 sheep. The findings demonstrated that *H. contortus's* FEC heritability varied from 0.39 to 0.48 and that there was a close genetic link between FEC following an initial and subsequent infection by the same and distinct species. With *T. colubriformis*, a comparable heritability (0.47) was discovered and the genetic connection within and across species was close to 1. Studies conducted by the author suggested that the number of fecal eggs might help select sheep that are resistant to nematode parasites (19).

Genetic differences among Breeds

For financial reasons, sheep breeders are particularly interested in the genetic heterogeneity in resistance levels to internal parasites across different sheep breeds. It is a known fact that some sheep breeds are more resistant than others to worm infestation. The author for instance, shows that local sheep from the Gulf Coast are more resilient than sheep from Suffolk County. According to the author, compared to local *Sumatra ewes*, imported *St. Croix ewes* in Indonesia have greater resistance to the parasites. Comparing Indonesian Thin Tail sheep to Merino and Fat Tail sheep, the former shows an extremely high degree of both innate and learned resistance to *Fasciolagigantica* and increased ability to withstand *H. contortus*. Red Maasai sheep were reported by the author to have higher immunological markers and lower FEC than Dorper sheep, suggesting that they are more resistant to *H. contortus* following artificial parasite infection.

Two separate crossbreeds, Nali X Lohi (Munjal) and Nali X Corriedale (Hisardale), each produced seven lambs with varying degrees of sensitivity to *H. contortus* infection, were examined by the author. Following an artificial infection with *H. contortus*, they discovered that Munjal lambs had a much higher peripheral *eosinophil* count and that *Hisardale* lambs had less body weight increase, hemoglobin and packed cell volume.



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They conclude that experimental H contortus infection can severely affect *Hisardale* lambs more compared to Munjal lambs and they advise more research on these genetic differences in vulnerability using a suitable experimental methodology (20). According to research by the author, gastrointestinal nematodes that are renowned for their procreation are less likely to harm Garole sheep.

Genetic Resistance Mechanism

According to the author, genetically resistant sheep are becoming a more attractive option for raising animal output and discovering novel resistance mechanisms not seen in commercial breeds (21). Crucially, parasitic gastrointestinal nematodes might not be able to adjust these defense systems of sheep that are specifically chosen. The processes behind sheep's genetic resistance to gastrointestinal nematode infections are, however, unclear. The number of worms and their length are demonstrated to positively correlate with fecundity. Studies that suggest the early stages of parasitic larvae as the focus of immunity and show minimal direct influence on the surviving adult populations describe very strong correlations between parasitological parameters. Sensitive sheep fight helminths during their early parasitic larval stages, whereas resistant sheep use a more prominent method to combat adult worms. Profound inflammatory mediators like histamine are released by these recruited cells, along with metabolites of arachidonic acid such as prostaglandins and *leukotrienes*. Along with strong vasodilators like *bradykinin*, these mediators most likely work to kill worm larvae by contracting nonvascular smooth muscle as well as causing plasma protein to sheep into the abomasum and intestinal lumen.

Genetic indicators for infection resistance against gastrointestinal nematodes

Hemoglobin type was initially employed as a genetic marker to select for resistance. Sheep possess two hemoglobin alleles, A and B. Animals with hemoglobin type AA exhibited more resistance against *H. contortus* infection than AB, which in turn showed greater resistance than BB. As indicators of *H. contortus* resistance, these hemoglobin types might not be very useful. Utilizing a candidate gene strategy to examine major histocompatibility complex (MHC) variability was the second effort. The multi-gene carrier complex (MHC) is made up of several closely related genes that convey antigens to the immune system of vertebrates. The complex exhibits very high levels of variability at a few genes.

Sheep have distinct class I and II regions on their MHC, which is incompletely understood when compared to other farmed animals. Immune protection against macro-parasites is thought to be influenced by the highly polymorphism sheep MHC class II gene. It has been found that there are allelic variants in the sheep MHC class II region at the DQA1, DQA2, DQB, DRA and DRB loci. The antigen binding groove of the produced protein is encoded by exon 2 in genes A and B, as well as the region with the greatest amount of sheep polymorphism. The (22) reported utilizing probes to measure a DQB and DRB class II genes' polymorphism in restriction fragment length (RFLP) in ovine MHC, but there was no evidence of a genetic link to parasite resistance. Sheep's MHC-DRB gene contains an expanded microsatellite region next to intron 2. The exon two variable and intronic microsatellites both showed evidence of allele segregation areas using the Single-strand conformational polymorphism (SSCP) approach.

Investigation of candidate genes

This review identified biologically significant genes that directly and indirectly regulate how the disease under study is treated to develop that are known as candidate genes. It has been demonstrated that the genes are linked to disease and they are more likely to be associated with the specific features of the disease. The main concept is to examine the mutations in animals that are vulnerable or resistant to an illness and in various breeds that have varying susceptibilities. Breeding for disease resistance can benefit from using a marker allele derived from mutations discovered in these genes. For this kind of polymorphism and ensuing association studies, molecular markers, particularly Single Nucleotide Polymorphism that show DNA-level polymorphisms, are employed (23).



Gene associated with Major Histocompatibility

The majority of vertebrates carry the Major Histocompatibility Complex (MHC) gene family. It is crucial for the immune system, autoimmunity and successful reproduction. A particular type of white blood cell recognizes the antigen shown by proteins expressed on any aspect of cells by the MHC that are encoded by this gene. This white blood cell is able to eliminate infections, diseased cells and dysfunctional cells or to organize their destruction.

A correlation was observed between the MHC-DRB1 allele and the number of fecal eggs in Scottish Blackface sheep after a spontaneous *O. circumcinta* infection. The discovery of nineteen DRB1 alleles in the intron between exons two and three (24) raises the possibility that the MHC complex is crucial to the establishment of resistance to *O. circumcinta*. They used five microsatellite markers to examine MHC variation in Soay sheep. The genes expressed and non-expressed in MHC class II contain the identifiers OLADRB and OLADRBps, respectively, whereas the MHC class I region has the marker OMHC1 along with the flanking markers BM1818 and BM1815 are employed.

They discovered that alleles related to parasite resistance in lambs and yearlings are associated with the OLA-DRB gene, which has a high correlation with the survival of juveniles. Yearling survival is greater and parasite resistance is stronger in the OLADRB 263 variation, whereas lambs with reduced parasite resistance and worse survival rates had a substantial correlation with the OLADRB 257 allele. Based on the findings, the parasites most certainly contribute to the population's ability to maintain MHC variety.

Receptors that Toll-Like Receptors (TLR)

Innate immune system components known as TLR are crucial. According to (25), TLRs are a set of ancient genes that are present in plants, invertebrates and vertebrates. It is well known that dysregulation of TLRs leads to an increase in unregulated inflammation and metabolic syndrome, which atherosclerosis, rheumatoid arthritis and cancer, among other chronic diseases, additionally to their role in defense against pathogens. A potential genetic marker for the relationship between bacterial infections and host immune responses in mastitis has been identified as the TLR gene family. This gave rise to the moniker Toll-like receptors for human proteins that share structural similarities utilizing *Drosophila larvae's* TOLL-cell surface receptor. The TLR family's first member to be discovered was the Drosophila Toll (dToll). The Drosophila toll protein is essential for host immunity against fungal infection and has been demonstrated to have a role in the establishment of the dorsoventral pattern in fly embryos.

One year after the Drosophila Toll was discovered, a human equivalent was discovered, which forms the lipopolysaccharide receptor complex with the CD14 molecule. There are up to 14 TLRs known in various species; they can both be recognized by the host as components made of bacteria RNA-IDNA and classified as having no known function. Humans, along with mice, have conservations like TLR1, TLR9. While TLR11 to TL.R13 are found in mice, TLRI0 is expressed in humans. There are ten TLRs known to exist in cattle genomes and each TLR can identify a different PAMP. The author looked at TLR4 in the Murrah buffalo population in an attempt to sequence nucleotides and find SNP using PCR-RFLP. Twelve SNPs in all, six of which were non-synonymous and caused an amino acid change, were found by multiple alignment analyses of the sequence data. The Basic Local Alignment Search Tool (BLAST) showed that the sequences of *Bosindicus, Bostaurus, Capra hircus, Ovisaries and Homo* sapiens shared 97, 97, 99, 98 and 80% of their homology, respectively.

The author determined the homologous identicality of cattle's TLR4 mRNA compared to animals. They found that the percentages of identification with sheep, pigs, humans and mice were, respectively, 98, 83, 80 and 72%. The TLR4 protein percentages homology that were found in cattle compared to sheep, pigs, humans and mice were 96, 81, 75 and 66%, respectively. They used nine primers to study the polymorphisms in TLRs and the results showed eight SNPs. In their investigation of haplotype variation, they discovered the TLR4 gene



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favorably selected ligand-binding sites in cattle of various breeds. Out of the thirty-two SNPs identified, twentyeight are located in the coding area.

Antigen-presenting cells and other immune cells express toll-like receptors, which are essential for identifying invasive infections. Multiple TLR genes, including TLR4, were demonstrated to be elevated in the gastrointestinal tract of resistant sheep with T. colubriformis and H. contortus infections. Susceptible people in the same research had lower levels of this gene's expression. TLR4 expressed more in the mesenteric lymph nodes of vulnerable Angus yearlings with Nematodirus spp., Ostertagia and Cooperia infections than in sheep. Numerous loci are probably involved in controlling resistance to gastrointestinal parasites like *H. contortus*. Several immune response mechanisms are employed to manage H. contortus in sheep.

CONCLUSION

This review identifies the resistant individuals through certain indicator qualities that would make the development of a disease resistance population more feasible. Including genetic components in disease management plans has several benefits, such as greater resistance to multiple diseases, consistency in resistance and, once detected, persistent genetic alteration. It broadens the range of disease management approaches available. Understanding the genes that regulate the processes involved and the genetic makeup of domestic animals in disease pathology would make it much easier to apply genetic selection to livestock for disease resistance, which is both innate and adaptable. The ability to apply marker aided selection to improve selection accuracy in breeding programs is made possible by the discovery of genetic markers. This information might contribute to an improved comprehension of the host's resistance and susceptibility mechanisms to gastrointestinal nematodes. These have the beneficial effects of lowering the dosage of anthelmintic medications, cleaning up the pasture and slowing the development of anthelmintic resistance. The creation of novel genetic markers for use in genetic improvement initiatives is one of the numerous benefits that uses of comprehending the genetic and molecular foundation of disease resistance.

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