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Manaswini Mandal

MVSc Scholar, Department of Animal Breeding and Genetics, College of Veterinary Science and Animal Husbandry, Orissa University of Agriculture and Technology, Bhubaneswar, Odisha, India

Chinmoy Mishra

Assistant Professor, Department of Animal Breeding and Genetics, College of Veterinary Science and Animal Husbandry, Orissa University of Agriculture and Technology, Bhubaneswar, Odisha, India

Sushant Kumar Dash

Professor, Department of Animal Breeding and Genetics, College of Veterinary Science and Animal Husbandry, Orissa University of Agriculture and Technology, Bhubaneswar, Odisha, India

Priyanka Priyadarshini

PhD Scholar, College of Veterinary Science and Animal Husbandry, Chhattisgarh Kamdhenu Vishwavidyalaya, Anjora, Durg, Chhattisgarh, India

Siddharth Sankar Sabat

MVSc Scholar, Department of Animal Breeding and Genetics, College of Veterinary Science and Animal Husbandry, Orissa University of Agriculture and Technology, Bhubaneswar, Odisha, India

Lipilekha Swain

MVSc Scholar, Department of Animal Breeding and Genetics, College of Veterinary Science and Animal Husbandry, Orissa University of Agriculture and Technology, Bhubaneswar, Odisha, India

Madhumita Sahoo

MVSc Scholar, Department of Animal Breeding and Genetics, College of Veterinary Science and Animal Husbandry, Orissa University of Agriculture and Technology, Bhubaneswar, Odisha, India

Correspondence

Manaswini Mandal

MVSc Scholar, Department of Animal Breeding and Genetics, College of Veterinary Science and Animal Husbandry, Orissa University of Agriculture and Technology, Bhubaneswar, Odisha, India

Genomic insight to the disease resistance in goat

Manaswini Mandal, Chinmoy Mishra, Sushant Kumar Dash, Priyanka Priyadarshini, Siddharth Sankar Sabat, Lipilekha Swain and Madhumita Sahoo

Abstract

The aim of any animal breeder is to get maximum possible profit from the domestic livestock. But due to the disease outbreaks it cannot be achieved properly. This can be effectively achieved by the study of genetic control of resistance and genetic variations to various diseases like gastro intestinal nematode, natural coccidiosis, Scrapie, PPR etc through appropriate measures. The integrated studies of combining quantitative and functional genomics, large-scale data collection (both within and between breeds) and epidemiological prediction will lead to new opportunities for breeders to select goats for enhanced resistance to a variety of diseases. Genetic variations through their effects on gene expression and protein function underlie disease susceptibility in small ruminants. The variants are in the form of SNP, deletion/insertions of nucleotides or whole genes, gene or whole chromosomal rearrangements, gene duplications, and copy number polymorphisms. The knowledge about genetic variations and function of different genes related to susceptibility and disease resistance will facilitate the incorporation of the information for the improvement of health status in the small ruminants.

Keywords: Disease, gene, goat, ruminant

Introduction

One way to meet the challenge of feeding galloping rise in population is to rapidly improve productivity and resource utilization (i.e. efficiency) in livestock farming systems. Small ruminants participate in the subsistence of a large human population and provide tangible (cash, milk, meat, fiber and manure) and intangible benefits (prestige, saving, insurance, cultural and ceremonial purposes). The key for sustainability of tropical small ruminant farming systems is to search for a balance between the environment and the animal. It is in vain to avoid constraints in animal rearing and wiser to choose animals for their adaptations to these constraints. The genetic material in animal harbors a rich collection of variations with either useful or harmful consequences on health and productivity. These variations are usually in the form of single nucleotide polymorphisms (SNPs), deletions/insertions of nucleotides or whole gene, gene or whole chromosomal rearrangement, gene duplications, copy number polymorphisms and copy number variations. In India, about 135.2 million goats are present out of which 28 genetically well characterized indigenous breeds. Chemical control of diseases is not effective in livestock due to drug resistance and concerns about the drug residues in food chain and environment further limit drug use (Bishop & Morris, 2007) [20]. So selection for disease resistance on genetic basis may be helpful as an alternative approach. Although positional and functional candidate genes related to host resistance and immune response have been identified in different species, they have not been amply explored in goats.

Candidate gene strategy has been proposed by direct search for quantitative trait loci (QTL). A total of 271 candidate genes have been detected in goats with passable effect on economically important traits. Some genes have synergistic or antagonistic effects in nature for expression of phenotypic traits. The identification of genes that influence the biological response to diseases would provide a better understanding of the physiological processes of the susceptibility to infection and immune response which could contribute to the development of genetic tools to fight diseases. Genetic variants have been explored to explain differences in host resistance. Before being efficiently used within breeding programs, the genetic information should be extended to whole populations and other breeds to accurately describe these marker associations, additive effects, and their marker-quantitative trait locus phase relationships.

Genetic resistance to diseases in goat Gastrointestinal nematode (GIN) Infection

Gastrointestinal nematode (GIN) infection is a major problem in the small ruminant industry worldwide. The susceptibility to nematode infection seems to be related to genetic factors, and resistance may vary among breeds. Comparative studies have shown that goats are more susceptible to gastrointestinal nematodes than sheep. Recommended drug dosage to goats are the same as for sheep but due to differences in the pharmacokinetics of drugs between sheep and goats, the anthelmintics are less efficacious in goats and may lead to rapid selection of anthelmintic resistant worm.

The major histocompatibility complex (MHC) is a candidate gene considered important for the immune system and disease resistance traits. The major histocompatibility complex (MHC) is a cell surface molecule involved in antigen presentation by glycoprotein receptors (Dukkipati, Blair, Garrick, & Murray, 2006) ^[10, 12] of immune cells (B lymphocytes, Dendritic cells, and Macrophages). MHC is divided into 3 subgroups such as MHC class I, MHC class II and MHC class III. MHC class I and class II encode heterodimeric peptide binding proteins but MHC class II can encode proteins that modulate antigen loading in lysosomal compartments. MHC class III encodes other immune compartments such as complement components, cytokines and heat shock proteins (HSP). The length of MHC I in goats is 1,077 bp encoding a mature protein with 337 amino acids. MHC class II molecules can be separated into DQ and DR subtypes and probably play a major role in the development of MHC restricted immune responses. In ruminants, the DRB is the most polymorphic locus of the MHC gene complex (Andersson & Rask, 1988) ^[2] having significant association with the resistance to nematodes (Axtner & Sommer, 2012; Buftkamp, Filmether, Stear, & Epplen, 1996) ^[3, 6].

The DRB1*1101 exon 2 encodes the β 1 domain, which makes up part of the PBR (peptide binding region) of the DR molecules. The residues found in this region have close contact with the peptides that are presented in the PBR or the TCR (T-cell receptor) region (Brown *et al.*, 1993, 2015) ^[4, 5]. Therefore, this region(s) is likely to have role in disease resistance or susceptibility (Buftkamp *et al.*, 1996) ^[6]. Gene expression of the DRB1*1101 was elevated in meat breeds of goat after exposed to *Haemonchus contortus*. Gene expression was highest in Boer goats, lower in Myotonic goats and lowest in Spanish goats. Gender differences in DRB1*1101 expression were observed where males showed higher expression than females (Corley & Jarmon, 2012a, 2012b) ^[8, 9]. Age differences influenced DRB1*1101 gene expression. The DRB1*1101 allelic expression was higher in younger (4 yrs old) than older (> 4 yrs old). Overall, regardless of breed, DRB1*1101 expression was higher in naturally susceptible than in resistant groups of pasture infected goats when compared to each other. The packed cell volume was somewhat negatively (47%) correlated with DRB1*1101 expression, indicating that the DRB1*1101 was more correlated with susceptibility to *Haemonchus contortus* rather than resistance (Axtner & Sommer, 2012) ^[3]. Three genotypes in *TaqI* locus and two genotypes in *BsaI* locus were identified in MHC Class II DRB gene in Rohilkhandi goats. Both the loci were found to be in Hardy-Weinberg equilibrium (HWE). The high degree of variability at MHC loci is intended to be an outcome of balancing selection at this locus.

Studies in Kenya with *Haemonchus contortus* and in France with gastro-intestinal strongyles have shown the existence of

genetic variation in susceptibility of nematode infections in goats. However, in a study in Fiji very little genetic variation in mixed *Haemonchus contortus* and *Trichostrongylus columbiformis* infections in goats were found. The Thai Native goats were found to be more resistant to *Haemonchus contortus* for parasitological and blood parameters as they had lower eggs per gram of faeces (EPG), lower worm counts and low reduction in blood values compared to their Anglo-Nubian crosses.

Cytokines are small cell-signaling proteins that play an important role in the immune system, participating in intracellular communication. Four candidate genes of the cytokine family (IL2, IL4, IL13, and IFNG) were selected to identify SNPs that might be associated with resistance to gastrointestinal endoparasites in Saanen and Anglo-Nubian goats. Three of the ten SNPs were identified as significant ($P \leq 0.03$). They were found in intron 1 of IL2 (ENSBTA00000020883), intron 3 of IL13 (ENSBTA00000015953) and exon 3 of IFNG (ENSBTA00000012529), suggesting an association with gastrointestinal endoparasite resistance.

Coccidiosis

Coccidia infections are one of the major causes of kid mortality and they cause severe economic losses to goat production by affecting early growth phase of kids. Coccidiosis is caused by infection with *Eimeria* species and it is host specific. Sixteen *Eimeria* species have been described from goats, worldwide (Zajac & Conboy, 2006) ^[25]. The major coccidia species that were found in the semi-arid region of India were *Eimeria christenseni*, *Eimeria jochejevi*, *Eimeria ninakohlyakimovae* and *Eimeria arloingi* with reported genetic variability in resistance. Oocyst counts at 3 months of age were different between Jamunapari and Barbari goats and breed difference has previously been observed between crossbred and indigenous breeds of South Africa. The faecal oocyst count (FOC) at both 3 and 6 months of age was negatively phenotypically correlated with both live weight and live weight gain, in Jamunapari and Barbari goats. Therefore, the faecal oocyst count between 3 and 6 months of age should be considered for genetic susceptibility analysis. However, before implementing these results in a breeding programme it would be necessary to first estimate more precise genetic parameters in a larger population.

Peste des petits ruminants

Peste des petits ruminants (PPR) of goats is caused by the Peste des petits ruminants virus (PPRV), a morbilli virus in the family Paramyxoviridae mostly responsible for increased mortality in kids. Increased susceptibility of West African goats, especially dwarf goats, compared to their European counterparts have been documented. Differential susceptibility of goat breeds within India has also been reported. Strain specific virulence of PPRV has been reported when the same breeds of goats were experimentally infected and different breeds of goat have been shown to respond differently to infection with the same virus. The natural susceptibility to PPRV in goats could be attributed to several host-derived or virus-derived factors. One such host derived factor could be the differential presence or distribution of specific viral receptors in these species, such as the signaling lymphocyte activation molecule (SLAM) that has previously been observed to be associated with PPRV and other morbilli viruses such as measles virus and canine distemper virus.

Toll like receptors (TLR) are type 1 transmembrane proteins expressed in almost all cell types and activate the innate immune system upon sensing pathogen associated molecular patterns (PAMPs). Intracellular TLR that sense viral nucleic acids include TLR3 (double stranded RNA), TLR7 and TLR8 (single stranded RNA) and TLR9 (CpG motifs in DNA). The cell specific location and basal expression levels of TLR mRNA could indicate the natural PAMP load of that tissue as well the innate host resistance to pathogens. In addition to the differential expression profiles of TLR, ligand induced downstream cytokine profiles and/or levels could also play a role in the innate disease resistance. The goat TLR7 gene is 3.4 Kb long, with a 3141 nucleotide open reading frame (ORF), coding for 1046 amino acids. The sequence analysis revealed five nucleotide changes in the TLR7 coding region and two nucleotide changes in the 3' UTR. All the changes were synonymous and it is difficult to establish a correlation with specific SNP and altered susceptibility to PPRV in the goat breeds.

Scrapie

Scrapie is a fatal and infectious neurodegenerative disease manifested by accumulation of an aberrant isoform of the normal PrP (i.e. conversion of a normal cellular protein, PrP^C into an abnormal isoform PrP^{Sc}). The abnormal configuration is considered to be infectious and resistant to proteolysis. The occurrence of natural scrapie is strongly influenced by alterations in the host gene that encodes PrP. The susceptibility or resistance to scrapie is varied among goats depending on genotype of the host and infectious strain. The polymorphic sites of the PrP gene in goats at 142, 143, 154, 222 and 240 bp have been used to describe scrapie susceptibility. Only the polymorphic site at 142 bp was associated with an altered disease incubation period. In goats, several field studies already have identified coding mutations of the gene encoding the prion protein (I/M₁₄₂, N/D₁₄₆, S/D₁₄₆, R/Q₂₁₁, and Q/K₂₂₂) that are associated with a lower risk of developing classical scrapie. The haplotype 1 was the only haplotype observed in every breed examined. The haplotype 2 was common in all breeds except the Toggenburg and Myotonic breeds. The haplotypes 3, 4, 5, 8, 9, and 10 were observed only within dairy breeds. Other three PRNP variants have been associated with incomplete scrapie resistance and were observed in US goats. The M142 variant has been associated with extended scrapie incubation time and had previously been found in Saanen and mixed-breed dairy goats. Further study is necessary to demonstrate full genetic scrapie resistance before genetic approaches to goat scrapie and it can be helpful to current efforts in scrapie eradication.

Conclusion

Livestock genetic research aims to better understand the basis of genetic resistance to diseases. The analysis of the polymorphism of these genes plays a key role to establish genetically controlled variation of quantitative traits affecting phenotypic performance. Nowadays, the sophisticated use of molecular and quantitative information on an industry-wide scale will require robust systems that can cope with imperfect data as well as the development of selection indices to take full advantage of the information. The information utility from candidate genes in breeding programs has potential effect in accuracy of selection and increasing selection differences. The use of resistant breeds for selective breeding and genetic improvement within the breeds contribute

towards disease control. Therefore, the use of genetic resistance in the host goat has the potential to limit the effects of disease and can increase the profitability of farmer and simultaneously address issues of sustainable livestock production. Thus continuous search for disease resistant genes should be carried out as a future method of disease control and eradication programme.

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