

GENETIC VARIATION IN DISEASE RESISTANCE AMONG FARM ANIMALS

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Invited paper

Abstract: This background study paper reviews the results of scientific investigations involving genetic control mechanisms for resistance/tolerance in farm animals to specific viral, bacterial, parasitic and prion diseases. The paper presents the most prominent documented examples for resistance/tolerance in cows, sheep and goats, pigs and poultry. The importance of genetically heterogeneous populations is highlighted, particularly as they impact response to epidemics, their duration, lower mortality rates, etc. Genetic studies on resistance in farm animals to a variety of etiological infectious agents can be determined at three genetic levels of variation: species, breed and unique genetic variation among individual animals. Depending upon the etiology of disease and the available animal resources, strategies for developing genetic disease management can be developed at the following levels: selection of breeds that are particularly well adapted to the local environment, breeding methods which include the introduction of genes exhibiting genetic resistance/tolerance towards pathogenic organisms, and the selection of individual animals with a high level of specific pathogen resistance. The most recent epidemic zoonoses illustrate how important it has become to develop global mechanisms for control of zoonoses and consequently the vital role of veterinary services in disease control.

Key words: animal health, genetics, disease resistance, public health

Introduction

Livestock are important in supporting the livelihoods of livestock keepers, consumers, traders and labourers throughout the world. Diseases affecting livestock can have a significant impact on animal productivity and production, human health (diseases transmissible from animal to humans), and, consequently, on the overall process of economic development.

In the developed world, breeding has focused almost exclusively on characteristics such as the milk, meat, egg and fiber produced, with drugs as virtually the only disease management strategy. The result is a serious reduction in the genetic potential of our livestock populations to resist or to tolerate infection, while actually increasing the genetic infectivity of the parasites themselves – worms, bacteria and viruses.

In countries with well-developed intensive livestock production, 39 infectious diseases have been identified thus far that cause great economic loss in livestock production and also threaten animal welfare. Broadly viewed, these diseases likewise pose a threat to the ecosystem, bio-security and human health. Outbreaks of swine flu and hoof-and-mouth disease in Great Britain suggest the vulnerability of current systems of disease control and prompt further consideration of the problems involved in developing rational measures for control of infectious disease in domesticated animals. *Bishop et al. (2002)*.

The application of established methods for disease control, such as the use of chemotherapeutic agents, antibiotics, and the implementation of vaccination protocols, have most frequently had negative consequences by prompting variability among microorganisms and the appearance of drug-resistant strains, which has resulted further in serious animal healthcare problems (*Savić, 2007*). One of the prominent issues in the control of diseases with bacterial etiology is increased resistance to antibiotics, particularly prevalent in intensive management systems where antibiotics are used irrationally to manage symptoms of unknown etiology and subclinical forms of disease. As a consequence of widespread drug use, increased resistance of nematodes to anthelmintics has been observed. Additionally, viral disease management and vaccinations programs for domesticated animals are met with constant challenges since every new generation of vaccination protocols results in the discovery of new more virulent viral strains, as was the case with Marek's disease in poultry *Bishop and Mackenzie (2003)*.

Taking into consideration the negative impacts of widespread drug use and the related costs of treating infectious diseases, which is estimated at 30-35% annually, current strategies for increasing the level of bio-security and health management in populations of domesticated animals strives for not only more rational utilization of drugs, but also towards increasingly more sophisticated use of genetic methods in disease control among farm animal species *Gibson and Bishop (2005)*.

Strategies for developing genetic control of disease

From the perspective of veterinary medicine in developing breeding programs, it is very important to distinguish between the following two terms: **resistance** and **tolerance**. Resistance refers to the ability of a host to resist

infection, while tolerance signifies a condition in which the host is infected by the pathogen but displays very limited adverse effects. If the goal is to stop the spread of infection to another population, as with zoonoses, than resistance to a disease is far more advantageous than tolerance. Genetic investigations involving animal resistance to infections caused by pathogens of varying etiologies can be determined at three genetic levels: species, breed and individual animal genetic variation. The impact of genetic resistance towards a causative agent of disease is greatest in cases where all levels of genetic resistance act synergistically. For example, studies of differences in genetic resistance among species to the infective agents that cause footrot, indicate that goats display a greater resistance/tolerance to these causative agents than do sheep.

When considering the significance of resistance/tolerance at the breed level, the intrinsic evolutionary advantage of breeds that are adapted to an environment should be taken into account. In tropical regions, where extreme endemic diseases are widespread, due to their evolutionary roots, locally adapted autonomous breeds display a far greater level of genetic resistance and adaptation, as compared to imported breeds (*Savić, 1995*).

Individual variability and the identification of those individuals whose resistance to disease can be determined through clinical examination, or the use of genetic markers (marker assisted selection), represents the first step in the formation of genetic resistance within a population. Depending upon disease etiology and the available animal genetic resources, the strategy for advancing genetic control of disease can be established through the following initiatives: the selection of locally adapted breeds, the implementation of cross-breeding methods geared at introducing genes significant in the expression of genetic resistance/tolerance towards pathogens, and the selection of individuals highly resistant to pathogens.

Animal genetic resources and resistance to disease

The study and preservation of animal genetic resources, relies on the management of a database (the FAO DAD-IS system) that includes phenotype and genotype characteristics and other health criteria, such as resistance/tolerance within a population to a variety of pathogens. This database serves as the foundation for further research and the advanced use of genetic resistance factors to diseases. Based on data from FAO DAD-IS 2007, genetic resistance/tolerance to a variety of diseases, has been reported in 59 breeds of cattle, 33 breeds of sheep, 5 breeds of horses and three breeds of pigs, all of which confirms that certain breeds express greater resistance to a larger number of pathogens than others.

Cattle

Studies on genetic resistance in cattle is aimed at so-called *target* diseases, those that cause enormous economic loss or at investigations geared at developing management programs for implementation in regions where a particular infectious disease is endemic in character.

Table 1. Examples of disorders for which there is documentation evidence of genetic resistance or tolerance in cattle (according to the study paper No 18. Bishop 2002)

Species Infectious agent	Disease	Comment
Virus	Foot-and-mouth disease	Anecdotal breed effects. Possibly tolerance.
Virus	Rinderpest	Documented breed resistance.
Virus	Bovine leukemia	Strong evidence for MHC effects.
Bacteria	Paratuberculosis (Johnes)	Within-breed resistance variation.Nramp is candidate.
Bacteria	Mastitis	Genetic effects subtle but well established.
Bacteria	Tuberculosis	Within & between-breed variation in resistance. Nramp?
Bacteria	Brucellosis	Within & between-breed variation in resistance.
Bacteria	Salmonellosis	In vitro evidence from Brucellosis resistant cattle.
Bacteria	Dermatophilosis	Verified breed differences.
Bacteria	Cowdriosis (heartwater)	Historical field observations only.
Protozoa	Trypanosomosis	Tolerant breeds exist.
Protozoa	Theileria (Theileria annulata)	Breed differences, possibly tolerance.
Protozoa	Theileria (T. sergenti)	Combination of resistance and tolerance.
Protozoa	East Coast Fever (T. parva)	Breed differences, possibly tolerance.
Protozoa	Babesia	Breed differences, tolerance.
Nematodes	Helminthosis	Combination of resistance and tolerance.
Ticks	Ticks	Combination of resistance and tolerance.

It is well-known that mastitis represents one of the most frequent problems in cattle production and is responsible for huge economic losses (*Jovanović, 2004*). This crucial production issue necessitates research that strives to identify animals displaying genetic resistance to mastitis.

Within the cattle genome mapping project, candidate genes have been identified that play a role in the complex process of genetic resistance to mastitis. Studies have indicated that variability within the BoLA complex, found in cattle, provides an opportunity for identifying alleles that have either a significantly positive or markedly negative effect on the expression of resistance to mastitis (*Yongerman (2004), Ødegård (2003), Heringstad (2006)*).

Sheep and goats

Table 2. presents an overview of documented evidence for genetic resistance/tolerance to individual diseases in sheep and goats.

Table 2. Examples of disorders for which there is documentation evidence of genetic resistance or tolerance in sheep and goats (according to the study paper No 18. Bishop 2002)

Species Infectious agent	Disease	Comment
Prion	Scrapie	Variation in resistance dominated by a known gene.
Bacteria	Footrot	Variation in resistance and vaccine response.
Bacteria	Mastitis	Genetic effects subtle but well established.
bacteria	Paratuberculosis (Johnes)	Anecdotal evidence of within breed variation.
Bacteria	Dermatophilosis	Selection of resistance successful in Merinos.
Bacteria	Salmonellosis	Heritable within-breed resistance.
Bacteria	Cowdriosis (heartwater)	Breed tolerance.
Protozoa	Trypanosomosis	Tolerant breeds exist.
Nematodes	Helminthosis	Combination of resistance and tolerance.
Plathyhelminths	Liver fluke (Fasciola hepatica)	Combination of resistance and tolerance.
Flies	Cutaneous myiasis (flystroke)	Selection for resistance successful in Merinos.

Relatively detailed research has identified genetic resistance in sheep to parasites, such as *Haemonchus contortus*, *Trichostrongylus columbriformis* and *Ostertagija circumcinta*, which has further confirmed a significant correlation between the occurrence of certain parasitic diseases and particular loci on the OLA complex (chromosome 20).

In veterinary medicine, footrot in goats provides a classic example of how environmental control strategy can be used in disease prevention. Studies have revealed an extremely complex immunological response, which involves approximately 26 alleles at two gene loci of the OLA complex. Since it appears that a potentially large number of genes are responsible for resistance to footrot, genetic markers (DNA testing) that have been thus far identified, represent merely the first step towards the eradication of genetically vulnerable individuals from a population.

The emergence of prion disease, along with the identification of responsible genes, represents the newest challenge in the study of inherited

predispositions to disease in sheep. Several tests have been developed which identify those mutations that appear in individuals susceptible to scrapie. Relevant testing includes codons 171, 136, 141 and 154.

Pigs

Special effort has been placed in research of genetic resistance/tolerance to the most critical viral and bacterial diseases occurring among pigs.

Table 3. Examples of disorders for which there is documentation evidence of genetic resistance or tolerance in pigs (according to the study paper No 18. Bishop 2002)

Species Infectious agent	Disease	Comment
Virus	African swine fever	Individual animals survive epidemics.
Virus	Foot-and-mouth disease	Anecdotal breed effects. Possibly tolerance.
Virus	Atrophic rhinitis	Within and between breed variation in resistance.
Bacteria	Neonatal diarrhea	Major gene conveys complete resistance.
Bacteria	Postweaning diarrhoea	Major gene conveys complete resistance.

One example that illustrates how genetically resistance individuals have been favored during selection, involves the use of a commercial test for Porcine stress syndrome (PSS) (*Jovanović, 2005*).

Other example is genetic resistance to the causative agent of neonatal diarrhea in piglets. A receptor in the intestinal tract to which a particular strain of *E. coli* adheres, is also genetically determined, while a commercially available DR2 gene marker test allows routine identification of genetically resistant individuals, and a DR1 gene marker test further identifies those individuals susceptible to F 18 *E. coli*. The utilization of these tests during breeding practices has significantly increased genetic resistance in those populations where it has been implemented. *Efords (2000)*.

Poultry

Studies on genetic resistance to viral, bacterial and parasitic diseases in poultry have confirmed a high level of genetic control in response to specific diseases.

Table 4. Examples of disorders for which there is documentation evidence of genetic resistance or tolerance in chickens (according to the study paper No 18. Bishop 2002)

Species Infectious agent	Disease	Comment
Virus	Marek's disease	MHC resistance gene used in breeding programs
Virus	Infectious laryngotracheitis	Inbred lines differ in resistance. MHC genes involved.
Virus	Avian leukosis	Single dominant gene affects resistance.
Virus	Infectious bursal disease	Breed differences in resistance
Virus	Avian infectious bronchitis	Inbred lines differ in resistance.
Virus	Rous sarcoma	Selection for resistance successful. MHC genes involved.
Virus	Newcastle disease	Heritable differences in resistance long established.
Bacteria	Pullorum	Inbred lines differ in resistance.
Bacteria	Fowl typhoid	Inbred lines differ in resistance.
Bacteria	Salmonellosis	Well established resistance effects.
Protozoa	Coccidiosis	Inbred lines differ in resistance. MHC genes involved.
Nematodes	Ascaridia galli	Differences between commercial lines in resistance.

Within the MHC of poultry, haplotypes have been identified that correlate closely to individual animal responses to the presence of a virus. As an example, investigations of genetic resistance to the virus causing Marek disease, mortality was significantly lower in a haplotype B21 white Leghorn population, than in B19 haplotype individuals .

When investigating the influence of haplotype on tumor growth caused by the Raus virus, a highly significant correlation between haplotype and response to the virus was also found. Tumors grew at a significantly increased rate (progressor P) in individuals with the B24 haplotype as compared to individuals with the B2 haplotype tumors regressed (regressors R).

Investigations of genetic resistance to parasitic infections in poultry, determined that breeds varied significantly in their level of resistance to coccidiosis. Investigations of resistance to high doses (150,000 oocysts) of *Eimeria tenella* indicated significant differences among breeds of chicken, and that the greatest level of resistance was measured in the Fayoumi breed, which is bred under extensive conditions and was not subject to the demands of the selection process. It was also determined that individuals of the same breed can display marked differences in susceptibility to coccidiosis. This variability is especially expressed in the White Leghorn, which has led to the use of immunological response as criteria for breeding practices and has resulted in lines which display a high level of resistance.

The importance of genetic variability in the selection of animals resistant to disease

A number of research models have been established that indicate the importance of genetic diversity within a population as crucial to response during the spread of infectious disease. Genetic diversity is defined as the number of individuals within a population that exhibit resistance to infection (bacterial, viral or other). Special attention has been focused on the importance and possible advantages of heterogeneous genetic populations, particularly in terms of the complex responses they confer to epidemics, their duration, decreases in mortality, etc. *Stringbett (2003)*. Due to their genetic advantages when in responding to epidemics of catastrophic proportion, the maintenance of genetic heterogeneity in livestock populations is crucial to maintaining viable livestock practices and the preservation of biodiversity.

The most recent epidemics of SARS, Avian influenza virus H5N1, etc. demonstrate the global impact of zoonoses and the significant role veterinary service organizations play in the prevention, detection, diagnosis, surveillance, response and research activities related to zoonotic disease.

Genetička varijabilnost otpornosti farmskih životinja na bolesti

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Rezime

U radu je dat pregled rezultata proučavanja genetičke kontrole rezistencije/tolerancije proizvodnih životinja na pojedine virusne, bakterijske, parazitske i prionske bolesti. Navedeni su najbolje dokumentovani primeri rezistencije/tolerancije kod goveda, ovaca i koza, svinja i živine. Istaknut je značaj genetički heterogenih populacija u pogledu odgovora na epidemije, niži mortalitet, dužinu trajanja epidemije i dr.

Genetička proučavanja rezistencije životinja prema infekcijama različite etiologije definisana su na tri genetička nivoa koji se odnose na vrstu, rasu i individualne genetske varijacije. U zavisnosti od etiologije bolesti i raspoloživih animalnih resursa, strategija unapređenja genetičke kontrole bolesti može se zasnivati na: izboru lokalno adaptiranih rasa, primeni metoda ukrštanja sa ciljem da se introdukuju geni od značaja za genetičku rezistenciju/toleranciju prema patogenima i selekciji jedinki sa visokim stepenom rezistencije prema patogenima.

Nedavne epidemije zoonoza ukazuju na značaj globalne kontrole zoonoza i važnu ulogu veterinarske službe u suzbijanju ovih bolesti.

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