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Use of molecular markers to enhance resistance of livestock to disease: a global approach

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Summary
The improvement and utilisation of host genetic resistance to disease is an attractive option as a component of livestock disease control in a wide range of situations. This paper reviews the situations where genetic resistance of the host is likely to be a useful component of disease control and provides a framework for deciding whether genetic improvement of resistance is likely to be worthwhile. Discussion is focused on low-input production systems in the developing world, where disease resistance is particularly important. The authors propose an integrated strategy for the use of molecular markers in assessing genetic diversity and in utilising and improving host genetic resistance to disease. The integrated approach assures that there is value in the molecular genetic information whether or not it proves useful in genetic selection, a feature that should prove attractive to funding and executing agencies.

Keywords
Conservation – Disease resistance – Disease tolerance – Genetic diversity – Genetic epidemiology – Genetic improvement – Marker-assisted introgression – Marker-assisted selection – Molecular markers – Quantitative trait loci.

Introduction

Disease resistance is a particularly important attribute of livestock in low-input livestock production systems in the developing world (5). Resistance to infectious diseases is often the critical determinant of the sustainability of such systems, and improving resistance is perceived as a primary target for genetic improvement programmes. This paper considers the value of host genetic variation in resistance for the control of livestock infectious disease, and the authors address the specific question of how molecular genetic markers can play a role in the utilisation and genetic improvement of host genetic resistance. An integrated strategy is then proposed and developed for the use of molecular markers that generates multiple benefits that might prove attractive for application in various situations in the developing world.

Utilising and improving genetic resistance to disease

The role of genetic resistance to disease in livestock production: key issues

The control of infectious disease of livestock is currently achieved by a number of mechanisms, including:

– chemical intervention, such as anthelmintics for nematode parasite control, acaricides for tick control and antibiotics for the control of many bacterial diseases

– vaccination

– sanitation and disinfection

– culling, isolation and control of the movements of animal and/or animal products.

Disease control or management using host genetic resistance (i.e. exploiting genetic variation in disease resistance amongst hosts) is increasingly recognised as a key component of effective disease control, complementing or sometimes replacing existing strategies.

Breeders and agricultural industries in the developed world have a variety of incentives to genetically improve host resistance to disease. Host resistance to disease is a low-cost and usually sustainable approach to disease control. Increasingly, other measures are failing as parasites evolve to resist chemical or vaccine control measures. Important examples include the evolution of resistance to anthelmintics by nematodes in all major sheep-producing countries, the evolution of resistance to antibiotics by bacteria, and the evolution of resistance to vaccines by the virus causing Marek's disease. Also, legislative changes in many countries are increasingly restricting the use of antibiotics and other therapeutics in animal production systems. There are also examples of governments dictating breeding strategies to farmers, such as the programme to limit clinical expression of scrapie in sheep flocks in Western Europe, using selection for prion protein (PrP) genotypes associated with resistance to scrapie. (It remains to be seen whether the PrP alleles said to be associated with resistance to scrapie in sheep confer complete or partial resistance, or perhaps confer delayed onset of clinical signs of disease.)

In the developing world, the majority of poor farmers face all the pressures experienced in more developed regions but either cannot afford or do not have access to therapeutic and vaccine control. In their systems, the genetically controlled resistance of the host is a critical component of effective disease control.

A major question that will be addressed below is: what are the benefits of improving disease resistance? The benefits of improved disease resistance differ from the benefits of improved production traits, because animals may infect each other either directly or indirectly. Hence, the expression of disease status in individual animals is not independent of expression in other animals. Consequently, animal breeders need to widen their perspective to include the dynamics of disease and ask the question: what impact will changing host genotype have upon disease dynamics within the population as a whole?

Setting priorities for genetic improvement

There are many potential target diseases for genetic improvement. Indeed, there are many more diseases than can ever feasibly be addressed. Before embarking on a genetic improvement programme it is important to demonstrate that:

– a disease is being targeted for which genetic improvement is an effective, low-risk method of disease control

– there is sufficient genetic variation for disease resistance between or within breeds to allow effective genetic improvement

– there will be clear economic and social benefits resulting from the genetic improvement of resistance, allowing for the option of using other methods of disease control (which might be used as an alternative too, or in conjunction with, the use of host resistance).

Evidence for genetic variation in disease resistance

Before assessing the evidence for genetic variation in disease resistance, it is necessary to define what is meant by disease and disease resistance. Disease is often used to describe two distinct concepts: infection and disease itself. For the purpose of this paper, infection is defined as the colonisation of a host animal by a parasite, where 'parasite' is a general term to describe an organism with a dependence upon a host. Parasites will include viruses, bacteria and protozoa (pathogens or microparasites), as well as helminths, flies and ticks (macroparasites). Disease describes the side effects of infection by a parasite. Disease may take several forms – acute, sub-acute, chronic and sub-clinical – which may or may not be debilitating. An individual host may be infected by a parasite, but suffer little or no harm. This is known as tolerance. In contrast, resistance is the ability of the individual host to resist infection or control the parasite lifecycle.

For almost every disease that has been intensively and carefully investigated, evidence has been found for host genetic variation in either resistance or tolerance. However, it is often not clear whether the observed genetic variation is for resistance to infection, tolerance of infection or a combination of both. Bishop (2) and Gibson (11) give partial summaries of more than 50 diseases for which there is documented or strong anecdotal evidence of genetic variation in host resistance or tolerance among the major domestic livestock species. Well-known examples include Marek's disease in chickens, F4 and F18 *Escherichia coli* infections in pigs, and nematode infections, mastitis, dermatophilosis, trypanosomosis and theileriosis in ruminants. In most cases, there are breeding programmes that aim to select animals for enhanced resistance (or tolerance) to these diseases, and in the case of bovine dermatophilosis this has been spectacularly successful (19).

The distinction between resistance and tolerance becomes important when considering the impact of selecting for disease resistance, as described in the next section. In general terms, when genetic improvement is made in host resistance to infection, there will be an impact on the transmission of infection. Conversely, genetic improvement of tolerance may reduce clinical signs of disease, but may not reduce transmission of infection to other animals.

Assessing the benefits of selecting for disease resistance: the concept of genetic epidemiology

The consequences of genetic change in the resistance of a population of animals to an infectious disease depend upon the transmission pathways of infection (6, 7). Typical pathways are shown in simplified form in Figure 1. Not all pathways are relevant to all diseases, and some of the pathways may be considerably more complex than shown here. For example, pathway *c* may involve intermediate hosts.

In diseases that arise from a reservoir of infection outside the host population of interest, the transmission of infection from this reservoir may be 'continuous' or sporadic. Once infection is in the host population it may follow several transmission pathways. Typically, but not exclusively, viral or bacterial infections will be transmitted by direct animal-to-animal contact along pathway *b*, whereas macroparasitic (for example, nematode or arthropod) infections will be transmitted via some external host, vector or reservoir. There are many diseases where pathway *a* is important and continuous, and pathways *b* and *c* are non-existent or trivial in terms of the impact of the disease. Examples include trypanosomosis and mastitis caused by environmental contamination. Diseases where pathway *b* is critical, with sporadic infection from the reservoir (pathway *a*), include most viral diseases affecting livestock. Pathways *a* and *c* are critical for nematode infections in ruminants, where there is a continuous flow of infection between the host population and the reservoir, which in this case is the pasture.

The consequences of these infection pathways have been explored by Bishop and Stear (3, 4) for the case of nematode infections in sheep, and by MacKenzie and Bishop (16, 17, 18) for viral infections in pigs. Reducing transmission of infection along pathways *a* and *c* will lead to so-called Type III epidemiological effects, in which a virtuous cycle of reduction in infection and disease consequence can be achieved (7). Reducing transmission along pathway *b* will lead to Type II epidemiological effects (7), in which the outcome of the reduction of transmission is a reduction in the frequency and/or severity of epidemics.

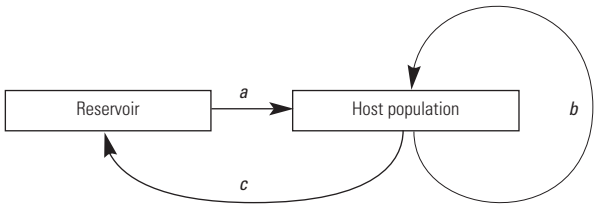

Fig. 1
Summary of different pathways of infection (*a*, *b* and *c*) for diseases in domestic livestock

These considerations indicate that the outcomes of selection should be measured at the population level, rather than the individual animal level. Moreover, the outcomes are very non-linear and depend upon the starting point. For example, a moderate improvement in animal resistance to viral disease might either solve the disease problem or make no impact at all, depending on the nature of the disease and the initial level of resistance of the host. A useful parameter for summarising this concept is the reproductive ratio, R_0, which is defined as the average number of secondary cases of infection resulting from one primary case introduced into a population of susceptible individuals. For example, if the primary animal infects five other animals, then R_0 is 5. As examples, scrapie probably has an R_0 only a little above 1.0, whereas foot and mouth disease (FMD) usually has a much higher R_0, well in excess of 10. R_0 has direct application in terms of defining genetically resistant populations of animals. In the case of genes that determine complete resistance, then the number of resistant animals that the population as a whole must contain is a simple function of R_0, as the requirement is simply to reduce R_0 below 1.0. These concepts are explored by Bishop and MacKenzie (6).

Genetic improvement which results in a reduction in the clinical signs of disease – that is, improved tolerance of infection – will be effective in reducing the incidence or the impact of disease in the target population. However, it may not decrease the prevalence of the pathogen. Hence, the disease incidence in other populations in the same environment will not be affected. In worst-case scenarios, the presence of infection in the environment may be masked by the absence of symptoms in the carriers of the pathogen.

Suitability of, and risks associated with, genetic improvement of disease resistance

Arguments developed from genetic-epidemiological concepts assist in the choice of suitable target diseases. For example, it is unlikely that breeding for resistance to FMD would be a viable strategy for the livestock industries in the United Kingdom (UK), even if it were possible. Because FMD has a high R_0, it would be necessary to have a high proportion of animals that were completely resistant to the disease before the population as a whole would be protected (i.e. before R_0 is reduced below 1.0). This could take many decades to achieve. In the meantime, any epidemic (from which the population would *not* be protected) would result in large-scale slaughter of animals under the current UK disease control strategy. In this example, current disease control strategies override genetic approaches.

For a zoonotic disease, it would be unwise to breed animals for apparent resistance if this apparent resistance were in fact

tolerance of infection. Such breeding would ignore the cause of the problem and merely hide the symptoms of disease, thereby potentially exacerbating the human health problem. This argument applies not just to pathogen species that cause both human and livestock disease, but also to some cases where livestock are not directly affected by the human pathogen species. An example might be the case of trypanotolerance in East African cattle, which are a major reservoir for the trypanosome species that cause human sleeping sickness. Improved tolerance to trypanosome species that cause trypanosomosis in cattle would reduce the need for treatment of the cattle with trypanocides. The consequently lower levels of treatment could in turn lead to higher levels of asymptomatic infection of cattle with trypanosome species, thus increasing the rate of human sleeping sickness.

The risk of parasite evolution

A common question is whether or not the parasite will evolve to overcome the genetic changes in the host. Absolute risks of parasite evolution are not easily estimated for any disease control intervention; the most important question is whether parasite evolution is more or less likely when genetic control strategies are used rather than other strategies? To answer this question, two types of genetic improvement can be identified:

– utilisation of resistance mechanisms that have evolved in indigenous breeds of livestock subject to endemic disease challenge for hundreds or thousands of years

– selection of disease resistance genes of unknown origin.

In the case of the disease resistance genes of indigenous breeds of livestock that evolved under endemic disease challenge, the mechanisms of resistance possessed by the breed will, by definition, be those that the pathogens have been unable to evolve resistance against. Such mechanisms are more likely to be resistant to future evolution of the pathogen. As such, utilisation of genetic resistance of indigenous livestock genetic resources has a high likelihood of having long-term sustainability and will be the application of choice where feasible.

Where genetic improvement involves selection for resistance genes of unknown origin, which are more likely to represent relatively new mutations that have not been tested by natural selection for their effect on the evolution of the pathogen, the outcome of the genetic improvement will be less certain. Aspects of these risks have previously been considered by Bishop and MacKenzie (6). There is insufficient space here to give detailed consideration to the sustainability of genetic resistance resulting from such selection, but some key factors are as follows:

– Disease control strategies that combine different approaches will generally be more sustainable, as parasites with a mutation allowing them to escape one strategy will still be susceptible to other forms of control. Thus, the combined use of host genetic resistance with other control strategies will often be more sustainable than use of any one control strategy alone. Also, host genetic resistance based on several genes will often be more sustainable than resistance based on a single gene.

– Genes that cause host resistance will place a greater selection pressure on the pathogen to evolve than those for host tolerance. Similar arguments can also be applied to specific aspects of resistance: risks are less if the resistance mechanism is reduced susceptibility to infection than if the mechanism is control of pathogen population growth or transmission.

– Selection pressures on the pathogen caused by host genetic resistance will usually be lower than with therapeutic or vaccine interventions. Therefore, host genetic resistance should be more sustainable than disease control interventions that place a strong selection pressure on successful parasite mutants.

– Pathogens with large population sizes and short generation intervals have the greatest potential to evolve in ways that defeat host disease resistance. Thus, host genetic resistance could be more sustainable for macroparasites such as nematodes than for viruses and bacteria.

– Genetic selection for improved disease resistance can be based directly on disease phenotype, on indicators of the state of the disease or on genetic markers for genes that cause disease resistance. Arguably, with genetic markers there is a danger that parasite evolution may go unnoticed and marker-based selection may be more risky. In practice, the greatest pressure on the pathogen to evolve will only occur after genetic improvement is widely disseminated in the livestock production system, so that use of molecular markers probably does not create a significantly greater risk of pathogen evolution than other methods of selection.

The use of molecular genetic markers in genetic improvement of disease resistance

Detecting and utilising genes that control disease resistance

Since the concept was first introduced in the 1970s, a large body of literature has accumulated on the theory of the use of molecular genetic markers to detect the presence of genetic loci controlling quantitative genetic variation: the so-called quantitative trait loci (QTL). Following advances in molecular genetic marker technologies through the 1980s and 1990s, this theory has been extensively put into

practice. In both livestock and model species, many hundreds of QTL have now been mapped. A substantial body of literature has also been developed on the theory of how to use molecular markers to select for QTL in genetic improvement programmes, both within populations and for introgression of QTL from one population to another. QTL are now being used in genetic improvement programmes for several species in the developed world. The general principles of the use of molecular markers in genetic improvement are covered elsewhere in this issue of the *Review* (see J.L. Williams); introductory reviews of the subject are also available elsewhere (1, 9).

When is it useful in genetic improvement to use quantitative trait loci that control disease resistance?

For traits that are easy to record and have high heritability, conventional phenotype-based selection methods will produce good genetic progress, and use of QTL is generally expected to yield only small increases in genetic progress or small reductions in costs. Use of QTL is predicted to be most beneficial for traits that have low heritability or are difficult, expensive or impossible to record. In this regard, use of QTL could be expected to be particularly beneficial in the low- to medium-input systems of the developing world, where the disease resistance and adaptation of livestock are critically important for the sustainable livelihoods of poor farmers. Disease resistance and adaptation traits are generally very difficult to record, and often have low heritability. Specifically, effective direct selection for disease resistance requires that:

– animals are exposed to disease

– the degree of challenge received by each animal can be recorded

– the response to disease challenge can be accurately recorded

– the disease exposure is ethically acceptable

– animals are capable of breeding efficiently after disease exposure.

Depending on the disease, achieving all of these conditions in a breeding programme may be difficult or impossible.

Assessing the impact of individual genes or quantitative trait loci

Studies aimed at detecting QTL for disease resistance will generally identify several different QTL with various effects on different disease phenotypes. For example, recent studies (26, 27) identified 14 QTL associated with various indicators of resistance to Marek's disease, including the proliferation of tumours, survival and viraemia. Similarly, Hanotte *et al.* (13) detected 16 QTL for various indicators of tolerance of trypanosomosis in a cross of N'Dama and Boran cattle. A critical question for the implementation of a breeding programme is: which of these QTL would be most effective in helping to control the disease?

Nath *et al.* (20) addressed this question using genetic-epidemiological principles to develop decision rules governing the likely value of QTL for resistance to viral diseases in intensively managed animals. The general principle of their decision tree is that different QTL will have different impacts on the overall transmission of infection, and those QTL that reduce the disease impact by considerably reducing susceptibility to infection are generally the most appropriate to use. Decisions on which QTL or genes should be the priority for research or utilisation purposes must be taken from the perspective of each individual disease.

Applications of molecular markers in the developing world

Although use of marker-assisted selection would seem to be particularly beneficial for improving disease resistance in the developing world, there is as yet no example of this technique being used in developing countries. In large part, the failure to use QTL information reflects the lack of investment in QTL mapping in the developing world. Such investment is needed not only to detect QTL that could be useful in genetic improvement programmes, but also to design improvement programmes, utilising QTL information, that would be sustainable under developing world conditions. The necessary investment is not easily obtained, because no coherent case has been made for a cost-effective and sustainable strategy for using molecular genetic information for genetic improvement in the developing world. A hypothesis-driven strategy for the use of molecular markers that has well-defined goals and would clearly make a difference to poor farmers could be attractive to both research and development-orientated funding agencies. The authors present here such a strategy for use of molecular genetic information to enhance genetic improvement in the low- to medium-input systems of the developing world. The strategy described below is summarised in Figure 2. It involves the use of molecular genetic markers to map genetic diversity among livestock breeds, to test hypotheses about which breeds carry unique QTL and to accelerate genetic improvement.

Mapping livestock genetic diversity

Over 6,400 documented breed populations of some 30 species of livestock have been developed in the 12,000 years since the first livestock species were domesticated.

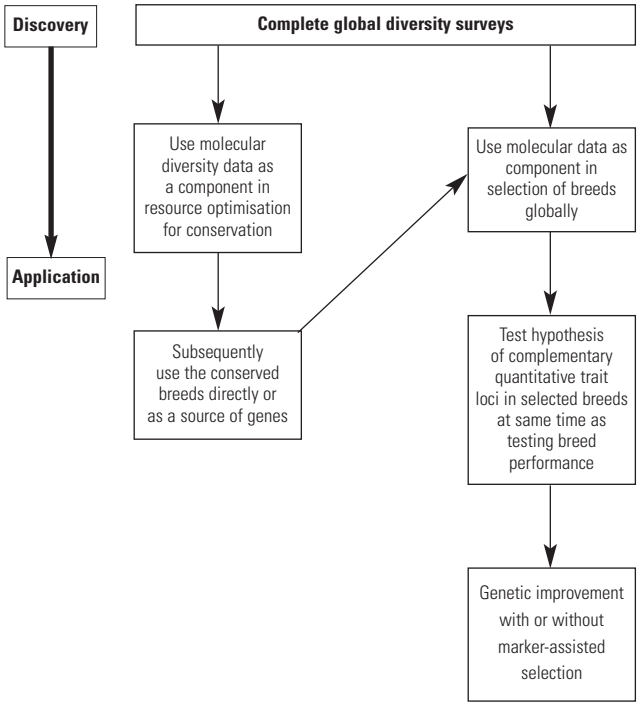

Fig. 2
Schematic of an integrated strategy for use of molecular marker information in the conservation and utilisation of livestock genetic resources

These breeds have evolved to allow livestock production in a wide range of situations, including some of the most stressful environments inhabited by humans. These naturally evolved genetic characteristics provide a coherent basket of sustainable solutions to disease resistance, survival and efficient production that have often been ignored in the drive to find technological and management solutions to individual problems of livestock production in low-input systems. It is estimated that 35% of mammalian breeds and 63% of avian breeds are at risk of extinction, and that one breed is lost every week. The performance, adaptation and disease resistance of the vast majority of breeds in developing countries have not been systematically recorded, and little of the information that does exist is in an easily accessible form. Moreover, the majority of livestock genetic diversity is found in the developing world, where documentation is most lacking and the risk of extinction is highest and increasing.

Molecular genetic markers can be used to estimate the genetic diversity within and between a set of breeds. Such information has been collected in a number of projects and used both to map the geographic distribution of livestock genetic diversity and to infer movements of livestock following domestication (12, 25). Such information is of great scientific interest. Until recently, however, it has not been clear how information on molecular genetic marker genotypes can contribute to the utilisation of livestock genetic diversity.

If the distribution of potentially useful genetic polymorphisms within and between the world's livestock breeds were known, objective decisions on the conservation and utilisation of genetic diversity would be relatively straightforward. In the absence of such genetic information, detailed phenotypic information could provide a very approximate guide to the underlying genetic polymorphism. But as noted above, even at the phenotypic level there is very little information on the production, reproduction, adaptation and disease-resistance potential of most livestock breeds. In this situation, information on genotypes at anonymous molecular genetic markers can provide valuable estimates of genetic diversity within and between populations, and this information can be used in decision taking for both the conservation and utilisation of livestock genetic resources. While the use of molecular markers may seem a diversion from the topic of improvement and utilisation of disease resistance, this technique forms an important component of an integrated strategy for the application of molecular genetic markers and as such the authors briefly describe how molecular markers can contribute to conservation decisions.

Use of molecular marker diversity in conservation decisions

Although the ideal would be to conserve all breeds of livestock for future potential use, the financial, physical and human resources are very unlikely to be available to do that. Decisions will therefore have to be taken on how to allocate finite resources for conservation. One goal of conservation will be to retain the maximum amount of diversity for potential future use. There is an almost complete absence of information on the distribution of potentially useful genetic polymorphisms among breeds, and only very limited information exists on phenotypes of developing-world breeds. In the short term, therefore, molecular marker information provides the most easily obtainable estimates of the genetic diversity within and between a given set of breeds.

Weitzman proposed a method for optimal allocation of finite resources for conservation to maximise the future inter-population diversity of wildlife species. This method has recently been adapted to conservation of livestock breeds (24) and extended to incorporate predictions of extinction probabilities (21) and to utilise combinations of molecular marker and phenotypic data (23). An alternative approach, designed to maximise a combination of genetic diversity within and between populations, has also been developed (10). These methods will require further development to deal with the complex reality of decision taking in conservation, but already provide a sound justification for collecting molecular marker data to map the global diversity of livestock species.

Use of molecular marker diversity in decisions on utilisation

Population genetics theory has long predicted that, under a given selection pressure, evolution will pick different genetic solutions in populations that are isolated from each other. Essentially, selection acts on the variation available, and this variation will vary between populations. The more genetically distinct are any two populations, the greater the likelihood that they will contain distinct genetic polymorphisms and the greater the chance that selection will lead to fixation of different genetic solutions to the same problem in the two populations. Experimental support for this theory exists in model species (14, 15), and most recently also for the case of trypanosomosis tolerance in livestock (13).

While there is enormous variation in levels of resistance to disease, there are many cases where no breed has achieved complete resistance. Trypanotolerance in cattle and gastrointestinal helminth resistance in sheep are good examples, where breeds exist that are able to survive and produce under disease challenge but still perform better in the absence of the disease. It would be desirable to produce animals with even higher levels of resistance to disease, which would be able to thrive under the highest challenge in the absence of other disease control measures. There are well-documented examples of several distinct breeds of a given species having evolved partial resistance to a given disease. Given the general lack of information on the characteristics of livestock breeds, there are probably many more undocumented examples. A good example is gastrointestinal parasite resistance in sheep, with at least eight breeds of sheep having been recorded as having some degree of enhanced resistance compared to exotic breeds developed in other environments.

In order to identify the best possible genotype for each of a range of production environments, the ideal situation would be to test all breeds with potentially useful characteristics, and all their crosses in each production environment. In practice such testing is not feasible, due to economic and logistical limitations, and increasingly also the difficulties imposed by issues related to sovereignty over livestock germplasm. What would be feasible in many cases would be to undertake testing of just two breeds from different countries. Many countries would see the advantage of a reciprocal exchange of germplasm with another country, which could overcome sovereignty concerns in many cases. Given that considerable time and money will be involved in the testing, the critical question is which two breeds would maximise the probability of being able to develop a better genotype. Obviously, choice of breeds will involve careful examination of existing data on breed characteristics and the environments under which they evolved. But where further improvement of a particular trait such as helminth resistance is desired, one consideration would be the likelihood that two breeds have evolved different mechanisms of resistance and that a higher level of resistance could therefore readily be developed from a cross between them. In this case breeders would seek breeds with suitable phenotypes, which are as genetically distant from each other as possible.

Use of molecular markers to confirm the hypothesis of different mechanisms of genetic control

Having brought two breeds together for testing in a given environment, on the hypothesis that they carry different mechanisms for genetic control of a desirable trait such as helminth resistance, it will be important to test that hypothesis before proceeding with a breeding programme. A suitable method for testing the hypothesis is to perform a genome-wide QTL interval mapping based on anonymous genetic markers in the F2 and/or backcrosses between the two breeds. Depending on whether or not the hypothesis is confirmed, the size of the QTL detected, the performance of the pure breeds and the F2 or backcrosses, an informed decision can then be taken on a suitable genetic improvement programme. The outcome might be to utilise one of the purebreds, to develop a crossbreeding programme, to develop a new breed through selection from crossbred or backcross populations, or to introgress QTL from one breed to the other. An informed decision can also be taken on whether or not the genetic improvement programme would incorporate marker-based selection. This decision will depend not just on the potential value of the marker information, but also on the cost and logistics of collecting and using the marker information in the genetic improvement programme.

Discussion

The proposed strategy for use of molecular markers is summarised in Figure 2. The important point is that molecular marker information is used as a key component of the decision-making process at all stages, including the final decision on whether or not further marker information will be collected within the final genetic improvement programme. A particular value of the approach outlined is that the QTL mapping is performed in the F2 or backcross populations that will almost certainly provide the foundation stock for the genetic improvement programme if a selection or introgression programme is decided on. Thus the whole process can, and should, be designed so that phenotypic data and QTL mapping results are obtained almost simultaneously, and the QTL mapping population can immediately be used to

initiate the genetic improvement programme. This minimises the costs of QTL mapping compared with undertaking an independent QTL mapping experiment, and ensures minimal delay between obtaining experiment results and implementing practical applications in terms of improved breeding stock for farmers. The latter feature should prove attractive to funding agencies that are primarily interested in achieving agricultural development objectives, while the hypothesis-driven nature of the QTL mapping should prove attractive to funding agencies primarily interested in biological research. Thus, the proposed approach to use molecular marker information has an additional advantage of being potentially attractive to a range of funding agencies.

A critical assumption that is not directly tested within the proposed strategy is that independently evolved genetic mechanisms controlling disease resistance will combine with some degree of additivity, so that higher levels of the desired phenotype can be selected from the crossbred population. Although this cannot be assured, there seems no *a priori* reason (unless the disease resistance appears to have reached a biological limit) to expect that there will be a complete negative interaction between the independently evolved resistance genes of the two breeds such that there is no advantage in having both resistance genes acting together.

A possible concern is recombination loss of heterosis in crossbred animals. This has been observed for fitness traits in crosses between *Bos taurus* and *Bos indicus* cattle, which Rutledge has argued (22) is most likely explained by the evolution of a high degree of positive epistatic interaction between fitness loci within the two sub-species over the more than 100,000 years since they shared a common ancestor (8). In the presence of large recombination loss, selecting an improved line from a crossbred population will take longer than the performance of the F1 would indicate. In such circumstances, the choice of genetic improvement programme will more likely favour the use of purebreds or a static crossbreeding programme than otherwise, and the potential value of the QTL mapping data is reduced. In practice, there is insufficient evidence to predict whether recombination loss will be a major problem when crossing genetically divergent breeds. There is, however, abundant evidence from many species that heterosis increases with genetic distance. This provides an added argument in favour of the use of molecular diversity data when choosing breeds for testing. Moreover, since performance data on the F2 and/or backcross will be required to estimate the degree of recombination loss, it makes sense to proceed with QTL mapping as outlined in the strategy until such time as recombination loss is shown to be a substantial problem.

In summary, this paper has presented arguments and evidence for the benefits of improving disease resistance, particularly in low-input livestock production systems. The authors have also presented an integrated strategy for utilising molecular markers to help assess genetic diversity, as a tool for designing disease genetics studies, and also for simultaneously detecting and exploiting genetic variation in resistance. This strategy could play a major role in understanding the genetic control of resistance to infectious disease and in solving practical issues that could potentially undermine the sustainable development of livestock production systems.

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Utilisation des marqueurs moléculaires pour renforcer la résistance des animaux d'élevage aux maladies : une approche globale

J.P. Gibson & S.C. Bishop

Résumé

L'amélioration et l'utilisation de la résistance génétique de l'hôte au processus pathologique constituent, dans des situations très diverses, un élément intéressant de la lutte contre les maladies du bétail. Le présent article examine les situations dans lesquelles la résistance génétique de l'hôte pourrait

représenter une composante valable de la lutte contre les maladies et fournit un cadre pour décider si l'amélioration génétique de la résistance peut s'avérer fructueuse. La discussion est axée sur les systèmes de production à faible apport d'intrants existant dans les pays en développement, où la résistance aux maladies est particulièrement importante. Les auteurs proposent une stratégie intégrée appliquée à l'utilisation des marqueurs moléculaires pour l'évaluation de la diversité génétique et l'utilisation et l'amélioration de la résistance génétique de l'hôte au processus pathologique. L'approche intégrée garantit l'intérêt des données de la génétique moléculaire, qu'elles s'avèrent ou non utiles pour la sélection génétique, caractéristique qui devrait être attrayante pour les organismes chargés du financement et de l'exécution.

Mots-clés
Amélioration génétique – Conservation – Diversité génétique – Épidémiologie génétique – Introgression assistée par marqueurs – Loci de caractères quantitatifs – Marqueur moléculaire – Résistance aux maladies – Sélection assistée par marqueurs – Tolérance aux maladies.

Aplicación de un planteamiento global en el uso de marcadores moleculares para incrementar la resistencia a las enfermedades

J.P. Gibson & S.C. Bishop

Resumen
La mejora y utilización de la resistencia genética de un huésped a la enfermedad constituye una opción atractiva como parte de la lucha contra las enfermedades del ganado en muy diversas circunstancias. Los autores pasan revista a las situaciones en que la resistencia genética del huésped puede ser un elemento útil para el control zoosanitario, y exponen una serie de criterios para decidir si merece la pena embarcarse en un proyecto de esta índole. Examinan sobre todo la situación de los sistemas productivos con pocos insumos de países en desarrollo, en los cuales la resistencia a la enfermedad reviste especial importancia. Acto seguido proponen una estrategia integrada de utilización de marcadores moleculares para estimar la diversidad genética y aplicar y mejorar la resistencia genética del ganado a las enfermedades. Este método integrado permite tener la seguridad de que hay información genética molecular valiosa, resulte o no de utilidad para la selección genética, algo que en principio debería interesar a los organismos tanto de financiación como de ejecución.

Palabras clave
Conservación – Diversidad genética – Epidemiología genética – Introgresión asistida por marcadores – Loci de rasgos cuantitativos – Marcadores moleculares – Mejora genética – Resistencia a las enfermedades – Selección mediante marcadores – Tolerancia a las enfermedades.

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