Livestock Science 166 (2014) 190–198

Contents lists available at ScienceDirect

Livestock Science

journal homepage: www.elsevier.com/locate/livsci

Genomics and disease resistance studies in livestock☆

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ARTICLE INFO

Keywords:
Genetics
Epidemiology
Infection
Tolerance
Infectious pancreatic necrosis
Bovine tuberculosis

ABSTRACT

This paper considers the application of genetic and genomic techniques to disease resistance, the interpretation of data arising from such studies and the utilisation of the research outcomes to breed animals for enhanced resistance. Resistance and tolerance are defined and contrasted, factors affecting the analysis and interpretation of field data presented, and appropriate experimental designs discussed. These general principles are then applied to two detailed case studies, infectious pancreatic necrosis in Atlantic salmon and bovine tuberculosis in dairy cattle, and the lessons learnt are considered in detail. It is concluded that the rate limiting step in disease genetic studies will generally be provision of adequate phenotypic data, and its interpretation, rather than the genomic resources. Lastly, the importance of cross-disciplinary dialogue between the animal health and animal genetics communities is stressed.

1. Introduction

Infectious disease is of major importance to livestock breeders for many reasons. For example, disease imposes a large cost on livestock production systems, with essentially all production systems being vulnerable to disease. Based on the direct costs of individuals diseases (e.g. Bennett et al., 2005), total disease costs have been estimated to be up to 20% of turnover in developed countries and as high as 35–50% of turnover within the livestock sector in the developing world. However, the true costs of disease are complex (Perry and Grace, 2009), depending on direct, indirect and intangible costs, which vary according to assumptions made about who is affected by the disease and the disease control measures. For example, infection may transmit across species. Several animal infections, such as bovine tuberculosis, pose zoonotic threats to human health, and diseases in one species may act as reservoirs for infections in other species. Additionally, there are pressures on breeders to address welfare issues and to reduce the reliance of production systems on control strategies such as extensive antibiotic and chemical usage, with regulation increasingly restricting antibiotic usage. For these reasons, rather than giving an actual cost, disease impacts are often considered to be a qualitative function of direct economic impact, industry and public concern, zoonotic potential and impacts on animal welfare and international trade (Perry et al., 2002; Davies et al., 2009).

Endemic infectious diseases pose particular challenges as these are diseases for which traditional disease control strategies, by their designation as endemic, are failing. Examples of worldwide importance include tick and nematode infestations, where there is widespread acaricide and anthelmintic resistance, respectively. Hence, alternative or complementary control strategies are required and breeding for increased host resistance to infection or disease is one such approach. Host genetic variation in disease resistance invariably exists, due in large part to the variability in host immune responses to infection (Bishop, 2010). Therefore, in principle, it may be possible to improve genetic resistance to most diseases, although ascertaining resistance phenotypes under field conditions can be challenging, as

☆ This paper is part of the special issue entitled: Genomics Applied to Livestock Production, Guest Edited by Jose Bento Sterman Ferraz.

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http://dx.doi.org/10.1016/j.livsci.2014.04.034
1871-1413/

described below. For a subset of diseases, it may be both feasible to measure resistance traits on sufficient animals to determine genotypes for resistance and economically worthwhile to incorporate such traits into breeding goals. A detailed appraisal of infectious diseases that may be amenable to host genetic studies, and potentially selection for resistance, is presented by Davies et al. (2009). In cattle, for example, this study identified mastitis as a key disease, as had been expected, however it also identified tuberculosis and paratuberculosis as amenable diseases, and recent progress on both diseases has been substantial (see below for tuberculosis).

A rate-limiting step in breeding for disease resistance is the requirement to measure resistance phenotypes. This can be costly and logistically difficult, and it is a significant barrier to selecting for disease resistance. For this reason, disease resistance traits are an attractive target for genomic studies and are often the subjects of such studies. The benefit of the genomic approach is the ability to select animals using DNA-based selection without the need to expose them to infection in a challenge test, or for them to have been part of a natural epidemic. This can be achieved if major genes or QTL for resistance can be identified, or SNP-chip based genomic predictors (Meuwissen et al., 2001) of sufficient accuracy developed. Without DNA-based predictions, selection accuracy will depend on either routine challenge testing or continuous disease prevalence in the field, to enable calculation of EBVs based on expressed resistance phenotypes.

This paper aims to consider some of the issues associated with using genomics to understand disease resistance in livestock, and using genomic tools to assist in breeding for enhanced resistance. We consider basic concepts necessary to understand the issues encountered with this topic and, in additional to a broad-level literature review, we dissect two contrasting case studies, where resistance may be considered to be either 'simple' or 'complex'.

2. Theoretical background

2.1. Resistance and tolerance

Terminology still causes confusion in this field. Firstly, the generic term 'disease resistance' is unfortunate as it implicitly confuses infection (invasion by a pathogen or parasite) with disease (the negative consequences of being infected). Resistance is best understood from an ecological consideration of the interaction between the host and the pathogen species (Grenfell and Dobson, 1995), may be defined as the ability of the host to exert some degree of control over the pathogen life cycle (Bishop and Stear, 2003; Bishop, 2012). This broad definition encompasses the many ways a host species may be more resistant (e.g., less likely to become infected, reduced pathogen proliferation once infected, reduced shedding or transmission of infection), and it also inherently recognises that resistance is usually relative rather than absolute. It also implies that altered resistance impacts on the population as a whole, as whilst some attributes benefit the individual host, other attributes (such as reduced transmission of infection) benefit other members of the host population.

Tolerance is different from resistance, and is discussed in depth by Doeschl-Wilson et al. (2012), and other papers in the Special Topic in Frontiers in Livestock Genomics (2012) on tolerance. Again using the definitions specified by Bishop (2012), tolerance may be defined as the net impact on performance of a given level of infection, i.e. the regression of performance on (a function of) pathogen load. A related concept, resilience, may be defined as the productivity of an animal in the face of infection. Whereas resistance implies a host exerting a deleterious influence on the fitness of the pathogen, hosts with a greater tolerance are those able to maintain a greater fitness as pathogen load increases. Definitions are presented diagrammatically in Fig. 1.

As a trait defined at the individual animal level, tolerance presents a number of difficulties and it also has a number of inherent assumptions that often seem to be ignored. Firstly, given that it describes the change in performance as pathogen load changes, individual animal performance has to be measured at different levels of pathogen burden, whilst at the same time keeping all other husbandry and environmental conditions as constant as possible. For most diseases this is problematic, especially as immune responses alter with continuing exposure to infection. In reality, it can probably only be measured at the individual animal level for traits expressed repeatedly through life and for diseases where the immune memory is weak. Some infections in lactating animals may fall into this category, for example mastitis in dairy ruminants or nematode infections during the peri-parturient period of compromised immunocompetence.

The issue of requiring different infection levels can be overcome to some extent by considering host genetics at the family level, so a sire's genetic merit can be observed as a reaction norm, with offspring with different pathogen burdens providing the necessary repeated observations. But even in this case, family size has to be sufficient to

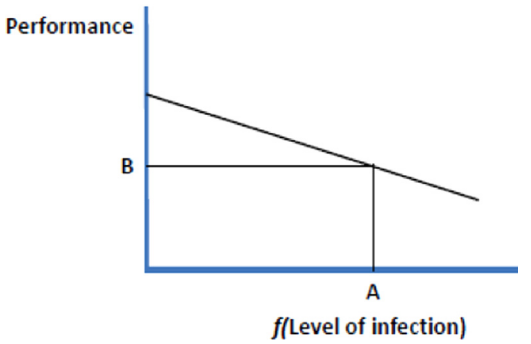

Fig. 1. Definitions used in the paper are: *Resistance* is the ability of the host animal to exert control over the parasite or pathogen lifecycle; *Tolerance* is the net impact on performance of a given level of infection; *Resilience* is the productivity of an animal in the face of infection. The figure (from Bishop, 2012) shows a schematic representation of performance and level of infection (or some function that linearises the relationship between level of infection and performance). The regression slope represents *Tolerance*, point A indicates *Resistance* and point B represents *Resilience*.