



Invited Review

Genomics to benefit livestock production: improving animal health

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ABSTRACT - The primary principle underlying the application of genomics is that it has the most value for difficult and expensive to measure traits. These traits will differ between species and probably also between markets. Maintenance of health will be one of the biggest challenges for efficient livestock production in the next few decades. This challenge will only increase in the face of demand for animal protein, resistance to existing drugs, and the pressure to reduce the use of antibiotics in agriculture. There is probably genetic variation in susceptibility for all diseases but little has been done to make use of this variation to date. In part this is because it is very difficult as well as expensive to measure this variation. This suggests that genomics should provide one of the ways of tackling the challenge of improving animal health. This paper will discuss the concepts of resistance, variation in susceptibility, and resilience; provide examples and present some recent results in cattle and pigs; and briefly discuss the application of gene editing in relation to disease resistance.

Key Words: animal breeding, disease, genome analysis, resilience

Introduction

Demand for animal protein is set to increase dramatically over the next few decades (FAO, 2002; Alexandratos and Bruinsma, 2012). This represents a significant challenge in terms of increasing productivity against a backdrop of reducing resources including land and water. It will require the application of many different technologies including genetic improvement (Ludu and Plastow, 2013). Whilst the largest cost of production is associated with feed, another significant element is the impact of disease. Indeed, the cost of disease may be underestimated due to its multifactorial nature and the relative success, up to this point, in controlling its impact, at least in the developed world. The role of genetics in improving animal health will become increasingly important as focus increases on tackling antimicrobial drug resistance (Bush et al., 2011) including the resistance to anthelmintics (Gilleard, 2013).

This challenge will also differ between species. A recent review (Raszek et al., 2016) provided examples from cattle. Here pigs will be used as the main example.

In pigs, large scale intensive production typically takes place in relatively controlled conditions in which

high health status is desirable and achieved through strict biosecurity, vaccination, and management such as all-in-all-out production. Genetic improvement is based on selection for performance potential in these clean environments at the top of the production pyramid. However, health status degrades as we go down the pyramid and there is a greater disease challenge at the commercial level. When disease occurs, one of the most important impacts, in addition to the cost of treatment and mortality, is the cost of morbidity, or, put another way, the impact on growth. This is an aspect that is sometimes ignored when people talk about disease resistance and genomics. There is a tendency to think of a bullet-proof animal, perhaps as a result of the success of vaccination, but also because there are examples of genetic resistance in which the animal is completely unaffected by a pathogen. Although there are some examples of genetic resistance to disease in livestock (see later), in most cases this is not achievable; instead, we should focus on reducing the impact of disease when it occurs and how genetics can impact this component of health: measuring and selecting for differences in levels of susceptibility.

This may also help us in terms of what diseases should be tackled using genetics and genomics. It will be impossible to tackle each specific disease through genetics. Instead, we seek to prioritize according to impact as well as the potential for variation in susceptibility. See for example, Davies et al. (2009), who looked at potential targets for several different species. The top-ranking problems were *Salmonella*, Marek's disease, and coccidiosis in poultry, bovine mastitis,

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and *E. coli* in pigs. Large scale efforts may also be justified in the case of a disease such as Porcine Reproductive and Respiratory Syndrome (PRRS), in which the prevalence, cost, and lack of success of alternatives suggest it should also be a priority. The latest estimate for the impact of PRRS indicates an annual cost of \$664 million to the United States industry alone (Holtkamp et al., 2013).

The next sections consider the difference between resistance and variation in susceptibility before going on to consider the concept of resilience.

Resistance

Disease resistance is a situation in which an animal remains completely unaffected by a pathogenic agent even when it is exposed to it. The most obvious example is when the target tissue or cells of an animal do not express the receptor that allows the pathogen to bind to cells as the first step of infection.

True resistance, as defined here, occurs for *Escherichia coli* (*E. coli*) associated scours in pigs. The majority of such scours across the world is due to two main groups: *E. coli* F18 and *E. coli* K88 (or F4). Unlike K88 scours, F18 only occurs post weaning. This is because *E. coli* binds to a specific receptor on the gut epithelium; however, the receptor is only present after weaning. This in part relates to the timing of the expression of the fucosyltransferase gene *FUT1*: when it is silent, all piglets are resistant to *E. coli* F18 (Meijerink et al., 2000). In addition, a polymorphism in this gene determines variation in the susceptibility of pigs to *Escherichia coli* F18 post-weaning (Meijerink et al., 2000; Frydendahl et al., 2003). Animals homozygous for the recessive resistant allele are completely resistant to infection by *E. coli* F18. Mortality from *E. coli* F18 in naïve herds can be very high (more than 20%). By selecting for genetic resistance to F18 by genotyping for the polymorphism and using homozygous-resistant boars, mortality can be immediately reduced. The level will depend on the frequency of the resistant allele in the sow herd. Importantly, in addition to reduced mortality, the growth of these pigs is significantly higher than the surviving pigs of the susceptible genotype. van der Steen et al. (2005) reported a difference in growth rate between the resistant and susceptible pigs surviving challenge of 0.07 kg/d ($P < 0.001$). In this case, it is clear that the benefit of breeding resistant pigs comes from reduced morbidity as well as mortality.

Selection for resistance can therefore be a very useful strategy when it is identified. Another interesting example is resistance to infectious pancreatic necrosis in salmon

(Houston et al., 2010; Bishop and Woolliams, 2014). The use of resistance will also depend on the availability of alternatives such as vaccination as well as the importance of the disease as it will be necessary to give up selection pressure on other traits. However, susceptibility to a disease is often much more complicated than the example of *E. coli* F18. Resistance of this type may not exist for a number of reasons; for example, the receptor may be essential for the normal development or function of the animal so that it cannot be lost.

Variation in susceptibility

Genetic variation in the susceptibility to infectious disease has been described as ubiquitous (see Bishop and Woolliams, 2010). These authors also point out that heritability may often be underestimated especially when it has to rely on field data to obtain enough data for its estimation. This relates primarily to different levels of exposure to the pathogen although other factors such as imperfect diagnosis may also contribute (see also Bishop and Woolliams, 2014). The use of commercial populations and field samples is gaining support despite the issues, and the potential of these approaches is set out in several excellent papers (Archibald et al., 2008; Bishop and Woolliams, 2010; Bishop et al., 2012; Bishop and Woolliams, 2014).

Although variation in susceptibility to most diseases can be observed, it is usually described as being polygenic and due to different mechanisms compared with resistance. See for example the case of tuberculosis in cattle (Allen et al., 2010). In these cases, all of the animals become infected, but the impact of the disease and the time to recover differs between individuals. Such differences could be related to the amount of the pathogen the individual is exposed to and the infectiousness of the pathogen, as well as many different management factors, but even when these aspects are well controlled, we still observe variation. The challenge experiments with porcine reproductive and respiratory syndrome virus (PRRSV) conducted at Kansas State University show this very clearly. The amount of virus produced by the animals and their growth varies greatly (Boddicker et al., 2012). Indeed, in some cases, the animals continue to grow as fast as uninfected controls. Similar results have been obtained with porcine circovirus 2 (PCV2) at the University of Nebraska (Engle et al., 2014). Heritability estimates across the PRRSV challenge experiments were 0.44 for viral load and 0.29 for weight gain (Boddicker et al., 2014).

Nowadays, we can use genome wide analysis studies (GWAS) to identify the genetic factors influencing this

variation. In the case of both of these diseases, the majority of the variation was polygenic; that is, a relatively large number of genes distributed across the genome are involved and each explain a small proportion of the variation observed. Even so, some regions have been found to explain a relatively large amount of the variation so that the variation could be termed oligogenic. For PRRSV, one region on chromosome 4 was found to explain more than 10% of the variation in viremia and growth after infection (Boddicker et al., 2012). The effect is dominant, so that only one copy of the beneficial allele is required to obtain the benefit. Excitingly, this effect was confirmed for a second strain of the virus (Hess et al., 2014), suggesting that it could be possible to select for pigs that are less impacted by PRRSV when it is present. Sequencing of blood samples from pigs showing different viremia and growth responses appears to have identified the causative mutation responsible for reduced susceptibility (Koltes et al., 2015). Other regions of the genome that were identified to influence susceptibility had relatively small effects (less than 2.6% of genetic variance for weight gain and less than 1.2% for virus load) (Boddicker et al., 2014).

In a separate study, a significant genomic component associated with PRRSV antibody response and the number of stillborn piglets was identified in an outbreak herd (Serao et al., 2014). The effect observed on antibody response was relatively large and suggests that response to vaccination may be a useful indicator of variation in the impact of reproductive PRRS. This aspect has been investigated by challenging pregnant gilts with the virus. Again, significant variation in response of individuals is observed, particularly in the status of fetuses at day 106 of pregnancy (Ladinig et al., 2014). Genome wide analysis studies and RNAseq studies are underway to investigate the genomic basis of the observed variation.

Challenge experiments with *Salmonella typhimurium* showed significant variation in fecal shedding of the bacterium. Some pigs persistently shed *Salmonella*, whereas others are able to clear the infection relatively quickly (Uthe et al., 2009). Again, this variation has a genetic component, suggesting it could be possible to improve food safety by selecting for pigs that more rapidly become non-shedders. In this case, RNAseq analysis of whole blood samples from persistent and low-shedding animals identified genes whose expression level was associated with variation in shedding (Kommadath et al., 2014). Furthermore, when blood taken from the same animals prior to infection was analyzed, this difference in gene expression was also present. This is an exciting finding, as it suggests that it may be possible to use this as

a phenotype to identify animals that will clear *Salmonella* much more rapidly when they become infected, so that the amount of *Salmonella* present in lairage can be reduced. This in turn would contribute to improving the effectiveness of post-mortem control of *Salmonella* contamination.

Something similar may be possible for *E. coli* O157 in cattle. Unlike the situation described for *E. coli*-associated scours in pigs (see above), *E. coli* O157 does not cause disease in infected cattle. Instead, cattle are asymptomatic carriers of the bacterium and are the reservoir for human outbreaks (Callaway et al., 2009). Some cattle are associated with greater levels of shedding of *E. coli* O157. The phenomenon is termed super-shedding and it has been suggested that it might be important as a target for control measures aimed at reducing future outbreaks (Chase-Topping et al., 2008).

Historically, vaccination has been the most effective tool for the control of infectious diseases in animals. While vaccination is important to the swine industry, not all vaccinated pigs go on to develop a protective immune response. Another option might therefore be to select for animals that respond more effectively to vaccination. Efforts are underway to use the next-generation sequencing approaches mentioned earlier to see if the early molecular interactions that control response to vaccination correlate with and are predictive of a protective immune response. Several regions of the genome have been found to be associated with variation in antibody production (reviewed in Uddin et al., 2010). However, Mach et al. (2013) did not find gene expression to be significantly affected in the blood of pigs with different levels of antibody following vaccination with *M. hyopneumoniae*.

Finally, recent results include the identification of regions of the genome explaining variation in susceptibility to bovine respiratory disease complex (Neiberger et al., 2014) and bovine tuberculosis (Bermingham et al., 2014).

Resilience

As noted in the introduction, it may not make sense to try to investigate the genetics of susceptibility for all diseases. An alternative may be to try to improve the ability of animals to respond to any infection in a way that minimizes the impact of the disease. This is now termed resilience, but is also sometimes referred to as robustness. This is the “big picture” view described in the road map proposed for the application of animal genomics for animal health (Archibald et al., 2008). Some of this group pointed out that it may be more productive to study many diseases in the same population than to conduct many smaller disease-specific

studies. This type of approach can be followed by utilizing field data making use of genomic tools to help address some of the problems in such studies. Alternatively, it may be possible to set up large challenge studies using mixed infections (Niederwerder et al., 2015) or by establishing a natural challenge by introducing different diseases using seeder pigs from different farms. The latter approach is being taken in an industry-academic partnership underway for pigs in Canada (Dyck et al., 2016; Plastow, 2016).

Whilst resilience has been defined as an aim for improving pig health for a long time, results have been mixed until now. Early work was carried out in Canada by Wilkie and Mallard (1999), who created a measure for immune response. However, despite initial promising results this did not, in the end, lead to a practical tool to improve the performance of pigs. One concern was that the pigs with the high response which were then selected displayed negative pleiotropic effects for other traits. Similar results were mentioned in relation to poultry. This did not stop others trying and a similar approach, but testing for better innate immunity was proposed by Clapperton et al. (2009). Again, promising results were obtained and these authors concluded that the “results suggest a role for using some immune traits...as predictors of pig performance under the lower health status conditions associated with commercial farms.” More recently, Wagter and Mallard (2007) developed an assay that is used to identify cattle that have superior antibody-mediated (AMIR) and cell-mediated immune responses (CMIR). These high responders have been shown to have a lower incidence of different diseases. For example, high-AMIR cows were shown to have lower occurrence of mastitis, improved vaccine response, and increased milk and colostrum quality (Wagter et al., 2000). These traits are heritable and most recently significant genetic variation in the traits was found to be associated with DNA markers on chromosome 23, which is the location of the major histocompatibility complex (MHC) in cattle (Thompson-Crispi et al., 2014). This offers the potential for incorporating this trait as part of genomic selection applied in dairy cattle. Another example, this time from sheep, points to the potential of relatively simple tests to identify animals that are able to better resist infection. In this study, a multivariate analytical approach using a single blood sample enabled the researchers to rank sheep in terms of their susceptibility to nematode infection (Andronicus et al., 2014).

Genome editing

A discussion of genomics and pig health would not be complete without including at least a brief mention of

genome editing. The development of this technology — a very precise way of introducing sequence changes — represents a significant change in possibilities including the potential to create animals resistant to disease (Lillico et al., 2013). Recent gene edits in pigs include the generation of GDF8 (myostatin) mutants to increase muscle, and constructs designed to provide resistance to diseases including PRRS and foot and mouth disease (Kang et al., 2014) as well as African swine fever virus (Lillico et al., 2013). This approach offers the potential to introduce new variation and opportunities for improving pig health. However, significant thought is needed in terms of the acceptability of the science and its application in terms of food production. Will consumers distinguish between gene editing and genetic modification? One of the advantages claimed for some gene edits is that they “leave no detectable footprint”. Whilst technically this may be a useful property, it may increase consumer resistance to the technology and products derived from it.

Conclusions

Variation in susceptibility to different swine diseases has probably been identified in all cases that have been investigated. There are clear examples in which it is possible to select for resistance to a pathogen, such as *E. coli* F18, which is responsible for edema disease, a significant problem in some regions. However, there are still very few examples in which genetics has been used to help improve pig health. Indeed, although there are some excellent examples in other species (e.g. infectious pancreatic necrosis in salmon), they are still few. One reason for this is the complexity of the trait: in most cases animals are not resistant to a disease; instead, they vary in their susceptibility to the disease agents. Although this offers the possibility of adding genetics to our toolbox, it is still difficult to demonstrate the potential of the approach. However, as indicated here, the difficulty in collecting the phenotype in field conditions contributes to an underestimate of the heritability of the trait. The opportunity for selecting for reduced susceptibility is therefore greater than is generally thought.

The availability of new high throughput genomics tools provides the opportunity to change this situation. Results from challenge experiments with PRRSV and PCV2 point to the potential to select for animals that continue to grow when faced with PRRS and porcine circovirus associated disease (PCVAD). The use of commercial populations and field samples is also gaining support despite the problems originally identified. In addition, the results from other species, including the most recent results obtained for

bovine respiratory disease complex and bovine tuberculosis suggest it may also be possible to select for animals that are more resilient in the face of disease challenge. This is an attractive approach, if it is successful, as it aims to improve the overall health of animals and to reduce the impact of infection by different disease agents. Although the concept is relatively old, we now have many more tools to explore the potential and to help understand the pros and cons of selecting for more resilient animals. We can also begin to look at the interaction between the environment and management (including nutrition) and genotype using these tools. For example, the gut microbiome may play an important role in the development of a successful immune response, and this may in turn be influenced by diet as well as the genotype of the animal.

Genomics comes into its own for genetic improvement when traits are difficult and expensive to measure. Without the development and application of these tools, progress will depend on routine challenge testing or continuous disease exposure in the field, which pose significant logistical challenges. This review describes how the use of large-scale studies including field trials can be combined with powerful genomics tools such as high density SNP panels and RNAseq to help dissect the variation that occurs in host/pathogen interaction and how this can help select for more resilient animals. The opportunity is clear and supports the need for increased efforts in this aspect of livestock improvement in order to meet the grand challenge of satisfying future demand for animal protein while also contributing to reducing the occurrence of antimicrobial resistance by selecting for healthier animals.

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