Disease Genetics: Successes, Challenges and Lessons Learnt

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ABSTRACT: This paper explores host genetic variation in resistance to infectious diseases in livestock, and the utilization of the results of disease genetic studies to breed animals for increased resistance. Issues surrounding the interpretation of field disease data are outlined and applied to two case studies, infectious pancreatic necrosis in salmon, where resistance is largely governed by a single locus, and bovine tuberculosis where resistance is heritable but polygenic. Lessons learnt are discussed, with emphases given to the need for the geneticist to understand the biology and epidemiology of the disease under consideration and fully engage with all stakeholders involved in disease control, including animal health experts. Disease resistance studies will continue to be of high priority to geneticists, with future challenges likely to lie in the provision of suitable phenotypes, and interpretation of these data, rather than provision of genomic resources.
Keywords: Resistance; Epidemiology; Livestock

Introduction

Infectious disease is of major importance to livestock breeders due to its cost, potential zoonotic threats, animal welfare issues, and threats arising from breakdown of currently used control strategies (e.g. anthelmintic and antibiotic resistance). Although predominant diseases vary between production systems, essentially all production systems are at risk. Endemic infectious diseases are particularly problematic as these are diseases where traditional disease control strategies are failing. In such cases, alternative or complementary control strategies are required, for example breeding for increased host resistance to infection (or disease) is a possibility. For these reasons, disease resistance is now one of the major targets of genetic or genomic studies in livestock.

Host genetic variation in disease resistance invariably exists, due in large part to the variability in host immune responses to infection, however not all diseases present themselves as good candidates for disease resistance studies. For example, some diseases result in immediate eradication attempts. Such diseases may include foot and mouth disease as well as avian influenza. For some other diseases the perception may be that existing control strategies are adequate, hence selection to increase resistance is not necessary. A detailed appraisal of infectious diseases that may be amenable to host genetic studies, and potentially selection for resistance, is given by Davies et al. (2009). Factors which influence the choice of a disease include its real and perceived importance, the likely benefits of increasing resistance and ease with which indicator phenotypes can be acquired. Gathering phenotypes requires exposure to infection and can be costly and difficult, making DNA-based selection attractive in many cases. Hence there is a growing popularity of studies that aim to find quantitative trait loci (QTL), genetic markers or genomic predictors for resistance.

This paper summarizes recent successes in disease genetic and genomic studies, and identifies key lessons learnt and thus pointers towards future success. Key concepts and outcomes are illustrated from my own research. The main focus is on specific infectious diseases, with concepts such as robustness and generalized immunity not covered in any detail in this paper.

Overview of the field

Many studies have investigated genetic variation in host resistance to an infectious disease: where studies have been sufficiently well powered, some indicator of heritable variation (e.g., breed differences, heritabilities, QTL, genetic markers) is invariably seen (Bishop (2010). Most likely, host genetic variation would be seen for all diseases, given appropriate experimental designs. Published examples exist for every class of infectious agent, ranging from TSE-causing agents, through viruses, bacteria, protozoa to worms, flies and ticks; and examples are seen across all major livestock species.

Genome scans by linkage disequilibrium (LD) are increasingly popular for disease resistance, but these studies tend to require a larger sample sizes than heritability or within-family QTL linkage studies. Performing studies of sufficient size can be costly and challenging. Consequently, for larger animals, the major focus has been on major endemic diseases in which data can be collected on commercial farms, notably tuberculosis (see below), paratuberculosis (e.g. Kirkpatrick et al. (2011); Minozzi et al. (2012)) and mastitis (Sahana et al. (2013)) in cattle, porcine reproductive and respiratory syndrome (PRRS) in pigs (Serão et al. (2014a and b); Orrett et al. (2014)), and nematode infections in sheep (Kemper et al. (2011); Sallé et al. (2012); Riggio et al. (2013)). Deliberate challenge experiments arguably give more precise data, but with the exception of PRRS (Boddicker et al. (2012)) these have seldom been feasible in larger animals. It is usually only for species with high reproductive rates and consequently low individual animal value (e.g., chickens, salmon) that deliberate challenge experiments are feasible on sufficiently large numbers to ensure reasonable experimental power. A chicken example for coccidiosis is given by Bacciu et al. (2014) and salmon examples are given below.

The main utility of studies which dissect genetic variation in resistance is that, hopefully, they lead to tools to breed animals for increased resistance – replicating what

natural selection has attempted for millennia in unmanaged animal populations. For many years, Marek's disease (MD), a viral disease in chickens, was used as a prime example. Genetic differences in MD resistance were first published by Cole (1968) with MHC involvement in resistance, specifically, the B21 allele (Briles et al. (1977). These results led to genetic management of MD in intensive poultry systems with selection on response to infection (Friars et al. (1972)) and specific B alleles within the MHC (Bacon (1987)). However, concurrent vaccination, whilst necessary, has most probably generated more pathogenic strains of MD virus following each new vaccine (Witter (1998)), leading to the situation where MD is now a 'hot' disease and more effective genetic control strategies are now needed. Mastitis represents a less dramatic situation, whereby breeding for mastitis resistance does not attempt to eliminate or prevent the disease, rather it recognises the endemic nature of the disease and attempts to control the mastitis incidence through the weightings given to mastitis resistance in the selection indices. Many breeding programs aim to hold mastitis incidence constant whilst improving other functional, welfare and productivity traits. In many sheep production systems, selection for nematode resistance represents perhaps one of the easiest scenarios where substantial genetic improvements in resistance can be made. This has been demonstrated under commercial conditions by Kemper et al. (2010), in which 15 years of selection for resistance led to 80% reductions in both worm burden and the indicator trait, faecal egg count, compared to unselected controls. Such reductions would dramatically alter the required disease management strategies, i.e. anthelmintic requirements. Lastly, research outputs can lead to quick and dramatic improvements in disease resistance, for example if major gene effects are discovered. This has been seen for single gene resistance to various *E. coli* infections in pigs, and it is detailed below for the salmon disease infectious pancreatic necrosis.

Epidemiological context for disease resistance

Disease resistance appears to be defined in many different ways by different researchers, and this leads to confusion. The concept is best understood by considering the disease biology and ecology (Genfell and Dobson (1995)). Infection may be defined as the invasion of a host by a parasite (or pathogen), and disease as the negative consequences of such infection. Resistance may then be defined as the ability of the host to exert some degree of control over the parasite (or pathogen) life cycle (Bishop and Stear (2003); Bishop (2012)). This encompasses the many ways a host may be more resistant (e.g., less likely to become infected, reduced pathogen proliferation once infected, reduced shedding or transmission of infection), and it implies that resistance is usually relative rather than absolute. It is also important to realise that changes in resistance are likely to impact the population as a whole, through the reduction transmission of infection (because an animal has a lower pathogen load or it is less infectious) to other members of the host population.

Tolerance describes the disease impacts of infection. Again using definitions from 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. Resilience is simply the productivity of an animal in the face of infection. The difficulties of describing tolerance at the individual animal level are discussed in depth by Doeschl-Wilson et al. (2012), with the issue essentially being that tolerance requires performance measurements on the same animals (or groups of animals) at different levels of infection or pathogen. Whilst Wilson et al. (2012) propose innovative solutions to this issue, and some diseases do allow repeated measurements (e.g., those during expressed during lactation), tolerance remains a difficult trait to measure at the individual animal level. The utility of tolerance for situations where disease prevalence is substantially less than one has also been questioned by Bishop (2012). By definition, expression of tolerance is dependent on animals being infected, and if prevalence is low then these infected animals will tend to be the least resistant animals. Therefore, the trait will be undefined for the more resistant animals, i.e. those that are of greater interest to the breeder.

Focussing on resistance; whilst field data, particularly from populations undergoing an epidemic, may be a cost effective means of obtaining data for disease genetic studies, there remain many issues associated with interpreting such data. Typically these are concerns raised by animal health experts and revolve around phenotype imprecision. They include incomplete exposure to infection, imperfect diagnostic tests and variable infection pressures over time and between environments. These influences will all tend to reduce heritabilities (Bishop and Woolliams (2010a)) and the power to detect SNP associations Bishop et al. (2012), as well as actual estimated SNP effects and the accuracy of the genomic predictions.

With incomplete exposure to infection, uninfected animals will comprise individuals that are resistant at the level of challenge they have encountered, as well as animals that have yet to be exposed to an infectious dose of pathogen. Incomplete exposure biases both estimated SNP effects and heritabilities downwards, with the former reduced by a factor ε, where ε is the proportion of the population exposed to the infection.

Diagnosis of animal health state introduces further uncertainty: specificity (S_p) is the probability that a truly *healthy* individual is classified by the diagnostic test as *healthy* (i.e. not infected by the disease-causing pathogen being studied) and sensitivity (S_e) is the probability that a truly *diseased* individual is classified by the diagnostic test as *diseased*. This parameterisation is universal in epidemiological theory. If either S_p or S_e is less than one, then observed prevalence (p') will differ from true prevalence by the regression: $p'=(1-S_p)+(S_e+S_p-1)p$. Imperfect diagnosis will reduce both heritabilities and estimated SNP effects, with the SNP effect biased

downwards by the factor (S_e+S_p-1) (Bishop and Woolliams (2010b); Bishop et al. (2012)). Joint estimation of diagnostic parameters and heritabilities from disease data is demonstrated by Nath et al. (2014).

The impacts of variable infection pressures on genetic parameter estimation are complex and have yet to be fully elucidated. They will vary according to whether infection pressure is presumed to be 'constant' but different in different circumstances/environments, or whether it varies dynamically during an epidemic. An example of the former is discussed below, in the salmon disease case study. The latter case is addressed by Lipschutz-Powell et al. (2014), with theory and examples for estimating major gene effects presented by Pooley et al. (2014).

The consequences of incomplete exposure to infection and imperfect diagnosis are that genetic signals are diluted and the power to quantify genetic effects is reduced. These factors probably contribute to the commonly-held belief that disease resistance traits are lowly heritable, an observation that is incompatible with the near-ubiquitous variation seen in immune-related genes and in immune responses (Bishop (2010)).

Case study for simple inheritance

The salmon viral disease infectious pancreatic necrosis (IPN) illustrates the application of genomic technologies to an infectious livestock disease and the benefits of parallel research by independent groups (in Scotland and Norway). It is also one of the first implementations of DNA-based selected for disease resistance. The IPN virus is a double stranded RNA virus affecting both juvenile fry and seawater stages of the salmon lifecycle. In freshwater, fry are susceptible before the immune system is developed, and hatchery mortality losses in fry can reach 70% or more (Roberts and Pearson (2005)). In seawater, susceptibility coincides with the stress of smolting and seawater transfer, at ca. 15 months post hatching, with mortality ranging widely, i.e. anywhere from zero to >90% (Moen et al. (2010)).

Creation of many large full-sib families is feasible in salmon, allowing for robust genetic and genomic studies. These large-scale studies established heritable variation in IPN survival at the smolt stage under field conditions (Guy et al., 2006, 2009; mean h^2=0.43), and in deliberately challenged fry (Wetten et al. (2007); mean h^2=0.31). Microsatellite-based QTL studies performed on salmon smolts under either natural challenge (Houston et al. (2008)) or deliberate challenge conditions (Moen et al. (2009)) demonstrated that nearly all the observable genetic variation (in IPN survival) could be attributable to a single QTL on linkage group 21. Follow-up studies on fry, using deliberate challenges on large numbers of fish from a wider range of families, confirmed that the same QTL also largely controlled IPN survival in the fry (Moen et al. (2009); Houston et al. (2010); Gheyas et al. (2010)). This cross validation of results between populations and life cycle stages promoted confidence in the results; it increased their precision and allowed both windows of susceptibility to be addressed simultaneously.

The Scottish and Norwegian studies showed a frequency of the putative resistance allele in the range 0.3 to 0.5, indicating that selection to increase the frequency of this allele would make a substantial impact on the population mean. The results described above allowed linkage-based marker-assisted selection (MAS) to be implemented by the breeding companies involved with the research. However, this approach required reassessment of linkage phase between markers and the putative underlying polymorphism every generation. A more effective and sustainable MAS strategy would ideally utilise population-wide LD between marker and causative mutation.

The absence (in 2010) of a reference genome or a dense SNP chip made identification of markers in population wide LD with the QTL difficult. This problem was solved through the use of RAD sequencing (Baird et al. (2008) applied to families previously used for confirming the IPN resistance QTL in fry (Houston et al. (2012)). SNP discovery by sequencing was used in families and individuals with well-defined QTL genotypes; after various filtering stages two SNPs were selected and genotyped on ca. 4000 fish from 200 related families from the same (discovery) cohort, and ca. 5000 fish from 200 families from an unrelated (i.e. validation) cohort. Results were consistent across both cohorts, with mortalities close to 10% for homozygous resistant fish, 20-25% for heterozygous and >50% for homozygous susceptible fish. These markers can now be used directly and reliably in breeding programs, although currently neither the actual causative mutation nor the mechanism of resistance is known.

However, despite the strong genetic effect, epidemiological factors still appear to affect the expression of resistance. For example, estimated heritabilities for IPN-related survival in seven environments (Guy et al. (2009)) increased as prevalence of mortality increased, even after correcting for the binary nature of the data by transforming to the underlying liability scale. However, when prevalence was assumed to be a proxy for exposure probability (i.e. ε), and the heritabilities were corrected for exposure (Bishop and Woolliams (2010a)), then the relationship between prevalence and heritability of resistance disappeared. Notably, the heritability of exposure-corrected heritability resistance coalesced around a value in excess of 0.9, consistent with the QTL controlling most of the variation in IPN-dependent mortality.

Further, comparing QTL mapping results (i.e. Moen et al. (2009); Houston et al. (2010); Gheyas et al. (2010)), in the studies with higher prevalence the resistance locus appears to be additive, whereas in the low prevalence studies it appears dominant. This observation was rationalised by Bishop and Woolliams (2010b), considering the consequences of dose-dependent expression of resistance. Resistance (susceptibility to infection in this case) may be re-defined as the dosage level at which an individual becomes infected (or affected). When dose-

response curves tend asymptotically towards zero mortality for negligible infectious doses, and towards a high mortality for high infectious doses, the apparent mode of action of resistance is a function of the infectious challenge level. Thus, one may expect to observe dominant, additive or recessive effects depending upon the disease epidemiology, even when the underlying liability is additive.

Case study for complex inheritance

The full complexities of understanding and dissecting resistance, when resistance is seemingly complex, are well illustrated for bovine tuberculosis (bTB), a bacterial disease caused by *Mycobacterium bovis*. bTB is particularly important in the United Kingdom (UK) and the Republic of Ireland (RI) where, despite five decades of efforts to control bTB, it remains an ongoing challenge. The primary means of control comprises compulsory testing of cattle followed by slaughter of test-positive animals, with total costs exceeding £275 million in 2010/11, alone (Abernethy et al. (2013)). Research into bTB resistance in the UK and RI has benefitted from parallel research programs in the same way as seen for IPN, with expertise, concepts and results shared, and the two sets of results essentially serving as cross validations.

It is impractical to perform large-scale challenge studies for bTB resistance, therefore it is necessary to capture data from the field, specifically surveillance data. Typically in the UK and RI, all cattle herds are tested regularly (e.g. annually), using a skin test, for the presence of bTB. Positive animals are slaughtered and examined for clinical evidence of infection or disease. The presence of skin test positive animals in a herd triggers more intensive testing which continues until the herd is bTB free. Data from this program are challenging to interpret because both the skin-test and the abattoir inspection diagnoses are imperfect and variable exposure to infection creates difficulties defining phenotypes (e.g., what is a 'control'?).

The skin test and abattoir diagnoses of visible lesions are both effective at diagnosing affected herds, but they are poor at diagnosing the state of individual animals. Under field conditions, whilst the skin test has a high *Sp* (i.e. >99%), its *Se* is somewhat lower at ca. 0.7 (de la Rua-Domenech et al. (2006)), possibly as low as 0.55 (Neill et al. (1994); Bermingham et al. (2011)). In other words, close to 50% of truly infected animals may be missed with a single skin test. Efficiency of diagnosis in the abattoir is also poor and *Se* may be below 30% (Bermingham et al. (2011)). Therefore, although one may have confidence that animals diagnosed as infected most probably are infected, many true cases will be misclassified unless multiple observations are available, and this incorrect classification will bias heritability and SNP effect estimates.

Exposure to infection is also problematic, but it can be addressed by trait definition and experimental design. Firstly, not all herds are affected at any point in time. Therefore, data should be restricted to herd cohorts within which cases occur, specifically multiple cases as single cases in a herd risk being either a false positive, or an animal imported whilst infected. Secondly, exposure impacts can be reduced by classifying a case as an animal that is **ever** diagnosed as positive, with controls being animals from outbreak herds that are **never** diagnosed as positive. This 'ultimate fate' model was used by Bermingham et al. (2009) and Brotherstone et al. (2010); these authors estimated heritabilities for ultimate fate, based on skin test results, of 0.14 and 0.15, respectively. For presence/absence of visible abattoir lesions, heritabilities were 0.18 in both datasets. Correcting for imperfect diagnostic sensitivities, these values rise to ca. 0.20 to 0.25. A case-control study from Northern Ireland (NI), in which cases were both skin test and abattoir lesion positive and controls were 'never-positive' cows from affected herds, yielded a heritability of 0.21 (Bermingham et al. (2014)).

Genome wide association studies have been completed on the RI and NI datasets (Finlay et al. (2012); Bermingham et al. (2014)), using the 50k and high density SNP chips, respectively. In both cases, loci affecting liability to infection were reported, however the strong impression gained from these data was that resistance was a polygenic phenomenon, controlled by many loci. Hence, the genetic control of bTB resistance may be considered to be truly complex, and in such cases genomic selection may be preferred to conventional MAS based on individual loci. Tsairidou et al. (2014) demonstrated using the case-control data from NI that genomic prediction of bTB resistance is possible in principle, with prediction accuracies closely reflecting expected values (Daetwyler et al. (2008)) given the dataset size, numbers of markers and presumed effective population size of the Holstein breed. Indeed in situations such as bTB, where the disease is endemic but not present in all herds/flocks, genomic selection is advantageous. Whilst conventional pedigree-based EBV estimation is possible, it relies on continual (logistically difficult) data collection from affected cohorts of animals, and EBV accuracies for animals only distantly related to those in affected cohorts will be poor. Once calibrated, genomic selection reduces many of these problems, as it allows EBV estimation for animals distantly related to those with phenotypes, and it facilitates the use of data captured from herds without pedigree recording.

The bTB results demonstrate that even given uncertainties in the data, coherent genetic messages can still be obtained, and routes to implementation (i.e., breeding for increased resistance) can be devised. However, challenges remain in the interpretation and analyses of bTB data. Firstly, the true impact of subtle differences in trait definition on genomic predictions have yet to be fully explored. Secondly, many concerns exist within the animal health community related to selection of animals on the basis of a diagnostic test which is a response to infection; these concerns have previously been encountered with selection for mastitis resistance using somatic cell count. The issue is that selection on a response to infection may potentially alter the measurable response to infection as opposed to resistance to infection, and hence may alter the properties of the test without necessarily changing

resistance. This concern can be addressed through analyses of actual test values in existing datasets, interpretation of the magnitude of heritabilities for different trait definitions, and prediction of likely selection intensities and responses to selection. Lastly, the impact of genomic selection for bTB resistance on prevalence of disease is unknown. This will depend largely on the basic reproductive value (R_0) for the disease; if R_0 values are close to the threshold value of 1.0, then small changes in resistance could have large impacts on realised disease prevalence, whereas for higher R_0 values selection may have little effect. This issue is made more complex in the case of bTB due to the presence of wildlife reservoirs, notably the badger in the UK and RI. Estimating likely changes in prevalence will require disease modeling combining host genetics and epidemiology, possibly including transmission of infection to, and from, the reservoir hosts.

Lessons Learnt

The combination of theoretical and experimental research outlined in this paper, as well as interactions with many different research groups, stakeholders and scientists from other disciplines, has led to several generic lessons.

1. *Success is possible*: The practical examples shown here for IPN, the experimental results for nematodes in sheep reported by Kemper et al. (2011) and the ongoing efforts by the dairy breeding industry to hold mastitis in check, show that addressing infectious disease through host genetics is possible. This mirrors natural selection and, to date, selection for disease resistance has yet to break down.

2. *Genetic variation in resistance is everywhere*: This statement is non-surprising to geneticists or immunologists, but it can be difficult for experts from other fields, if they lack training in genetics, to grasp. Further, viewpoints are often encountered that current animal genotypes are somehow 'optimal', with any alteration in resistance to a specific disease invariably having negative consequences on performance and resistance to other diseases. Published literature shows no obvious pattern in genetic relationships between resistance to difference diseases, or between resistance and performance.

3. *Genetic architecture of resistance is different for different diseases*: Examples are seen for many different architectures, from single gene variants to truly polygenic resistance. A pattern that does emerge is that resistance to long-term endemic diseases tends to be polygenic, whereas major gene (i.e., large QTL) effects are seen for 'new' viral diseases such as PRRS and IPN. This presumably reflects the length of time that natural selection has had to remove (or fix) gene variants with large effect.

4. *Data interpretation can be difficult*: Field data has many sources of noise, some of which only become explicable when an epidemiological perspective is considered. Inference from such data remains noisy, but the gloomy interpretation that disease resistance is a lowly heritable trait is incorrect. Most likely, underlying resistance traits are strongly genetically variable, but noise can cloud the picture. Analysis of such data, to extract maximum genetic information, is an active area of research.

5. *There is added value at the population level*: Although disease resistance is expressed by individual animals, the benefits are realised at the population level (often with win-win consequences). These concepts are well embedded in epidemiological theory, and their recognition can greatly assist geneticists.

6. *Not all diseases are worth chasing*: There are many diseases; it simply isn't feasible to investigate every disease, nor can more than a subset ever be addressed in a breeding program. Choose carefully.

7. *Success requires cooperation*: It is unlikely that progress will be made without full cooperation from animal health experts. Ensure that you (the geneticist) understand the disease and that they (the animal health expert) understand the genetics and what you are trying to achieve.

8. *Robustness may sometimes be a better option*: The discussion above assumed that there is a disease of overriding importance to be addressed. If this is not the case, yet animal health is an issue, then robustness (performance under 'dirty' conditions) may be a better option.

Where Next?

Disease resistance will continue to be a goal trait of importance to breeders and of interest to geneticists. The latter stems partly from the opportunities for high impact publications that geneticists crave. Genomic data and tools are unlikely to remain rate limiting steps for these studies, with the prospect of complete genome sequences available on many animals. However, geneticists must avoid the trap that seems to accompany every new technology, viz. the willfully naïve belief that this technology will solve all problems. Whilst valuable, sequence data will likely raise many new questions, which in turn will require new technologies. Combining diverse types of 'omics data, i.e. integrative biology, may help in some cases, e.g. for major gene effects. But where trait variation is genuinely polygenic it seems difficult to envisage fully understanding the impact of genetic variants with small effects on the trait.

The most important, and rate limiting, challenge for disease genetic studies is likely to be obtaining suitable phenotypes. Collecting and interpreting field data will be key, particularly when harvesting data from epidemics. This will require extensive communication with epidemiologists, who are numerically strong biologists who use similar statistical techniques to geneticists. However, geneticists often rely on cross-sectional data, whereas epidemiologists prefer longitudinal data often at the herd level with individual animal identification not recorded. Inter-discipline communication will greatly facilitate data collection, with a goal being to have data valuable to both groups and useful for many types of analyses. Developing

the techniques to further analyse and interpret these data will remain an interesting challenge for geneticists.

Acknowledgements

I wish to acknowledge funding from many sources, particularly the BBSRC, through specific projects and the Institute Strategic Grant, the EU, Defra and the Scottish Government's SPASE initiative. Industry inputs are also gratefully acknowledged, particularly from LNS, Genus and DairyCo for the examples cited herein. Many colleagues have made valuable contributions to this research, all of whom appear as authors on the cited papers.

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