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Genetic resistance to infections in sheep

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ABSTRACT

This paper considers genetic resistance to infectious disease in sheep, with appropriate comparison with goats, and explores how such variation may be used to assist in disease control. Many studies have attempted to quantify the extent to which host animals differ genetically in their resistance to infection or in the disease side-effects of infection, using either recorded animal pedigrees or information from genetic markers to quantify the genetic variation. Across all livestock species, whenever studies are sufficiently well powered, then genetic variation in disease resistance is usually seen and such evidence is presented here for three infections or diseases of importance to sheep, namely mastitis, foot rot and scrapie. A further class of diseases of importance in most small ruminant production systems, gastrointestinal nematode infections, is outside the scope of this review. Existence of genetic variation implies the opportunity, at least in principle, to select animals for increased resistance, with such selection ideally used as part of an integrated control strategy. For each of the diseases under consideration, evidence for genetic variation is presented, the role of selection as an aid to disease control is outlined and possible side effects of selection in terms of effects in performance, effects on resistance to other diseases and potential parasite/pathogen coevolution risks are considered. In all cases, the conclusion is drawn that selection should work and it should be beneficial, with the main challenge being to define cost effective selection protocols that are attractive to sheep farmers.

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1. Introduction

Host genetic variation in resistance to infectious disease is ubiquitous (Bishop, 2010) and is arguably a necessary consequence of the continued arms race between host and pathogen (Khibnik and Kondrashov, 1997). Natural selection has, for millennia, exploited such variation and led to the diversity of locally-adapted breeds that are seen in small ruminant production systems worldwide. What has been less appreciated is that animal breeders also have the opportunity to exploit between-animal genetic variation in resistance to assist with disease control, and ultimately produce animals that are healthier, more productive and require less intervention to control disease.

This paper reviews the evidence for genetic variation in resistance to various major endemic diseases in sheep (and goats) and considers the use of genetic variation in resistance for the purpose of breeding animals for increased disease resistance. However, selecting for disease resistance is often perceived as having various consequences or side effects in terms of effects on (e.g.) performance, resistance to other diseases or pathogen evolution. This paper also briefly considers these additional effects, assessing whether or not they are of concern for the diseases considered in this paper.

2. The nature and quantification of genetic variation

Most traits or phenotypic characteristics of importance in domestic livestock show considerable between-animal variability, with the observed differences between individuals being at least partially under genetic control. Furthermore, most traits are genetically complex insofar as observed genetic variation is the joint effect of variants (or mutations) at (or affecting) many genes. This is well illustrated for the example of genetic variation between lambs in resistance to infection by nematode helminthes as assessed by faecal egg count (FEC), in which many loci throughout the genome have been shown to contribute to the observed variation, all with a small effect (Kemper et al., 2011). Whilst examples are seen where variation at a single locus does have a large effect on the trait [e.g., scrapie resistance (Hunter et al., 1997) or litter size in sheep (Juengel et al., 2013)], these tend to be the exception rather than the norm.

Quantitative genetics is the science of quantifying genetic variation, i.e. determining the extent to which traits are under genetic control. The typical quantitative genetic parameter is the heritability, which describes the proportion of observed between-

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animal variation that is genetic in original. Formally, it is the regression of genotype on phenotype, and its value lies between 0 (no genetic control) and 1 (complete genetic control). Estimation of heritabilities also enables estimation of breeding values for individual animals, this being a predictor of the expected performance of the progeny of an animal.

Heritability and breeding value estimation traditionally required recording of pedigrees, i.e. sire (and dam) for each animal, preferably extending over several generations. Consequently, because they were limited to populations in which pedigrees were recorded, geneticists were also somewhat restricted in the phenotypic information available to them. For example, disease information is often quite limited on farms which record pedigrees, as these tend to be the better farms with fewer health problems and often active measures are taken to keep disease out, e.g., extensive use of vaccines or medicines such as anthelmintics. However, this situation has changed with the advent of so-called single nucleotide polymorphism (SNP) arrays or SNP chips (e.g., http://www.illumina.com/products/ovine_snp50_whole_genome_genotyping_kits.ilmn for sheep and Tosser-Klopp et al. (2014) for goats). These arrays can genotype animals simultaneously at many loci throughout the genome, typically ca. 50,000 in the case of sheep and goats. In doing so, it is possible to build up detailed profiles of animals, and conduct sophisticated genetic analyses of animals even in the absence of pedigree data (Meuwissen et al., 2001). Specifically, in the case of disease, this approach enables one to collect data from the site of disease outbreaks in the field, simply genotyping cases (affected) and controls (unaffected). Thus, genetic profiles can be built up using opportunistic data from commercial flocks/herds, e.g., for bovine tuberculosis resistance as reported by Bermingham et al. (2014) and Tsairidou et al. (2014). Such techniques can be used to identify major loci affecting a trait (e.g., Kijas et al., 2013) or to predict individual animal breeding values where the trait is seemingly polygenic (Tsairidou et al., 2014). Because of the power and utility of SNP chips, they have become increasingly prevalent in disease genetic studies in small ruminants, particularly since their introduction in sheep in 2010.

3. The role of host genetics in disease control

The existence of host genetic variation in resistance means that one can breed animals for increased resistance, at least in principle. Therefore, exploiting host genotypes for resistance can contribute to a disease control strategy. However, it is important to consider both the method of selecting animals, and the rate at which selection might proceed, as expectations can sometimes be naively optimistic.

Selection based on genetic markers associated with resistance is an attractive option, as it avoids the need to expose the animal to infection. This approach could be based either on a small number of markers each with a large effect on resistance (i.e. maker-assisted selection, or MAS) or on the combined effect of many markers using a SNP chip (i.e. genomic selection). Whilst MAS is often promised, there are very few cases in practice of successful MAS, mainly because it is difficult to find markers that are consistently associated with phenotypes across a population, i.e. are in population-wide linkage disequilibrium (LD) with causative mutations. Further, for widespread endemic diseases which have been present in livestock population for many generations, mutations with large effects on resistance are unlikely to be present as natural selection will have taken any variant with a large effect either towards fixation (for a beneficial effect) or loss (for a deleterious effect). In sheep, it is really only *PrP*-based scrapie resistance that convincingly shows consistent marker effects that can be used across unrelated animals. When resistance is due to the combined effects of variants at many genes, genomic selection is likely to be technically feasible, and indeed is now standard practice for mastitis resistance in dairy cattle. For sheep, genomic selection has been shown to have good accuracy for mastitis resistance (Duchemin et al., 2012) and nematode resistance (Riggio et al., 2014), but only when predicting resistance in closely related animals. However, the primary issue that would need to be resolved before genomic selection can be implemented is cost, as at current prices it is unlikely to be economically feasible to implement SNP chip-based selection in sheep.

As described above, with the exception of scrapie resistance, selection for disease resistance is likely to have similar properties to selection for any other complex trait, with rates of response depending on selection intensities applied when choosing parents and the rate at which generations are turned over. Consequently, typical rates of genetic progress may be 1–2% per year, up to 5% if the trait is especially heritable or variable. An excellent example is given by Kemper et al. (2010), in which FEC and worm burdens were reduced by 80% following 15 years of selection for reduced FEC under field conditions. With this degree of reduction it may be envisaged that these selected sheep no longer require frequent or active interventions to control the disease.

Genetic progress arising from selection based on either phenotypes or genomic predictions is cumulative, sustainable and very valuable, and forms the basis of most modern breeding programmes. However, it does not increase resistance immediately and hence it does not negate the requirement for other forms of disease control, at least not in the short term. Therefore, host genetics should always be considered as a component of an integrated disease control strategy, rather than as a substitute for other forms of control.

4. Evidence for host genetic variation

Davies et al. (2009) ranked livestock diseases in terms of their amenability to host genetic studies and, potentially, the use of selection to improve resistance to each of the considered diseases. For sheep, the top ranking diseases were mastitis, gastrointestinal nematode infections and foot rot. Here, the evidence for host genetic variation in resistance to mastitis and foot rot is considered, along with that for scrapie; nematode infections are outside the scope of this review.

4.1. Mastitis

In the study of Davies et al. (2009), mastitis was the top ranking sheep disease amenable for genetic studies. This is due largely to its importance in the dairy production systems, where sophisticated trait recording protocols can be implemented. In contrast, in meat production systems, trait recording for mastitis would be more challenging. Assessment of mastitis resistance in genetic studies is usually performed by using somatic cell counts, with increased cell counts employed as an indicator of infection and hence subclinical mastitis. Of course, observed clinical disease can also be recorded, but if its incidence risk is small, then it is a less useful trait and, additionally, it does not encompass the harmful impacts of subclinical infection. As well as indicating subclinical mastitis, cell counts also have value as indicators of milk (processing) quality, with producers often being penalised for increased cell counts in milk. Finally, in cattle, but not yet in sheep or goats, milk payment schemes take into account the somatic counts of milk delivered, hence any reduction in those numbers can have a direct beneficial effect on the farmers' income.

'Somatic cell counts' in milk refers to an invariably a heritable trait in sheep, with heritabilities generally lying in the range of 0.1 to 0.2 (Riggio et al., 2007). Evidence in goats suggests heritabilities for somatic cell counts that are possibly higher than for sheep (e.g.,

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