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REVIEW OF GENETIC PARAMETERS FOR DISEASE RESISTANCE IN SHEEP IN NEW ZEALAND AND AUSTRALIA

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SUMMARY

Genetic factors, mainly heritability estimates, have been reviewed briefly for all major disease traits affecting sheep production in New Zealand and Australia. The traits reported included resistances to nematode parasites, liver fluke, flystrike and fleece-rot, lice, mycotoxic diseases (facial eczema, ryegrass staggers, heat stress caused by ergovaline, and infertility caused by zearalenone), mastitis, foot rot and pneumonia. Selection lines have been under study for at least six of these traits. In general, all the traits are characterised by heritabilities of sufficient size that selection progress can be made, if it is cost-effective to carry out the scoring and apply selection pressure. Given the difficulty of scoring many of the diseases under field conditions, the advent of DNA marker technology could provide a large boost in the near future to reducing incidence of these diseases by breeding. The quantitative trait locus studies carried out will provide pointers to candidate genes controlling the expression of disease resistance traits. It is likely to be beneficial to investigate the underlying genes controlling each resistance trait, with a view to developing additional possible forms of disease control.

INTRODUCTION

Interest in breeding sheep for resistance to diseases has grown considerably over the last few decades. The famous textbook by Drs Helen Turner and Sydney Young (1969) contains only one reference to disease genetics in its index (associated with inbreeding depression), although there is a specific mention of fleece-rot. Since the 1970s, considerable research effort has been put into estimating genetic parameters for disease resistance traits in sheep, particularly in New Zealand and Australia. This has often been followed by analyses of correlations with production traits, and in some cases by attempts to introduce a disease test for use in industry flocks. There could be ethical and animal welfare issues associated with offering such tests, but equally there are issues about doing nothing, or about relying on drug treatments and other management strategies to remain effective for future generations.

This brief review will summarise genetic parameters, mainly heritability estimates, for some of the disease traits in sheep in New Zealand and Australia, with consideration given to the following disease groups: nematodes (including *Nematodirus*), other parasites (liver fluke, flystrike, lice), mycotoxic diseases, and some other diseases including fleece-rot, mastitis, footrot and pneumonia. Some of these areas have been covered fully in the past, whereas others have hardly received any attention. As recently as 2005, a review of Australian genetic parameters for sheep (Safari *et al.* 2005) included just two diseases, host resistances to endoparasites and to fleece-rot. Raadsma *et al.* (1997) described contemporary measurements of sheep for resistances to endoparasites, footrot, fleece-rot and dermatophilosis, the major diseases affecting Merinos in Australia, and they reported heritabilities and genetic correlations, described below. This paper attempts to cover the genetics of a range of diseases, regardless of industry-wide prevalence, because individual diseases may be highly relevant to just a group of farmers in one region, and this may create the demand for ram breeders in that region to apply selection.

RESULTS AND DISCUSION

Parasitic diseases

Nematodes. Host differences in susceptibility to endoparasites have been the subject of genetic studies in sheep for over 30 years. Following examples from early cattle studies (e.g., Frisch 1981), research groups attempted to monitor host-genetic variation in nematode parasite burdens via breed differences, then via genetic variation among sire groups, and then exploiting it via experimental selection lines. Many reviews have been published on the genetics of resistance to nematode parasites in sheep in New Zealand and Australia. Morris (2000) summarised published data on selection lines for high or low faecal egg count (FEC) in Romneys and Perendales in New Zealand, and in Merinos in Australia. In New Zealand there has also been a Romney line selected for high resilience (defined as the time to first drench post-weaning, whilst under nematode challenge, with acceptable growth rate and with minimal breech soiling). The realised heritability of the variously transformed functions of FEC listed in that report averaged 0.32 (with s.e.s, by experiment, ranging from 0.03 to 0.14), whilst the heritability of the measure of resilience to nematodes was 0.14 ± 0.03. More recently, Safari *et al.* (2005) have reviewed heritability estimates from many sources (published over the 1992-2003 years), and found a weighted average for transformed FEC of 0.27 ± 0.02, from 16 experiments. Heritabilities tend to be greater, on average, in experimental flocks than in industry data (Morris *et al*. 1995c), partly because of the greater degree of control of management in experimental flocks, and perhaps because of higher degrees of challenge to the animals. On the AAABG website (http://www.gparm.csiro.au; accessed 7 June 2009), there is still no summary of genetic parameters for this disease (or any other) in sheep.

In practical terms, host resistance to endoparasitism is now known as a heritable trait and is used in industry programmes: WormFEC in New Zealand, in collaboration with the recording scheme Sheep Improvement Ltd (SIL), and Nemesis in Australia. Genetic progress in FEC is being made in flocks where selection is applied, with heritabilities of ~0.2 (depending on FEC-sample timing) in New Zealand (M. J. Young, personal communication, March 2009), and 0.22 in Australia (Eady 2009). The next phase is to offer a DNA marker test or marker-assisted selection to breeders wishing to select for improved resistance, and the 'WormSTAR™' test [http://www.catapultsystems.co.nz/products/55_wormstar.cfm; accessed 7 June 2009], marketed by Catapult Genetics of Pfizer Animal Health, is now available to New Zealand ram breeders (but, at the time of writing, it is not yet validated for Merinos). In New Zealand, the WormSTAR™ marker explains approximately 2.3-3.6% of the genetic variation for the FEC traits, 4.8-5.5% of the live weight traits, 3.7% for the wool traits and 6.2% for lean weight (McEwan *et al.* 2008). Several studies have identified quantitative trait loci (QTL) for host resistance in sheep (reviewed by Dominik 2005). The interferon-gamma gene and haplotypes for the major-histocompatibility-complex have been identified in some studies, but not all. However, Crawford *et al*. (2006) noted that "Our failure to discover more QTL suggests that most of the genes controlling this trait are of relatively small effect".

Estimates of genetic correlations between FEC or transformed FEC and production traits appear to vary with breed and country, particularly estimates in coarse-woolled vs Merino breeds (e.g., Morris *et al*. (1997, 2000) in New Zealand, and Safari *et al*. (2005) in Australia). It should be noted that 'breed' is confounded with management /grazing conditions across countries, and sometimes also with parasite species involved in the parasitism, and with method of challenge (artificial vs natural; single-species vs mixed-species). The New Zealand papers cited show evidence that FEC is genetically correlated unfavourably with lamb growth, and with fleece weights at all ages, whereas the Merino data reviewed by Safari *et al.* (2005) suggest no significant

genetic correlations of FEC with lamb growth or fleece weight.

By anti-parasite antibody studies, Green *et al*. (1999) have shown in New Zealand that mixed-species challenge during the genetic selection process has led to host resistance to various individual parasite species. In Australia, Eady (2009) has shown for the *Haemonchus* selection lines that there is effective cross-resistance to different parasite species.

Heritable resistance to *Nematodirus* species has also been reported (Morris *et al*., 2004), with heritability estimates of 0.15 ± 0.03 in lambs of 4 months of age and 0.26 ± 0.04 at 6 months of age, with genetic correlations of these with FEC data recorded at the same ages having a weighted average of 0.43.

Liver fluke. The epidemiology of fasciolosis, or infestation by the liver flukes *Fasciola hepatica* or *F. gigantica*, has been reviewed by Spithill *et al.* (1999). Early studies established that genetic factors (breed differences) were involved in host resistance to each species: whilst many sheep breeds were susceptible to *F. hepatica* (including Merinos), some were resistant to *F. gigantica.* The latter worm species is of primary concern in tropical countries, but the host's liver metabolism in response to *F. gigantica* is perhaps of wider interest, as presented below. Raadsma *et al*. (2008a) reported the development of a predictive index of *F. gigantica* worm burden, including the use of cathepsin L5 antibody titre, eosinophilia, and the activity levels of serum enzymes secreted during parasitic injury to the liver: glutamate dehydrogenase (GDH), and injury to the bile duct: gamma-glutamyltransferase (GGT). Studies with the Indonesian Thin Tail breed, which appears to carry a major gene for resistance to *F. gigantica* (Roberts *et al*. 1997), have since led to the identification of 12 QTL for host resistance using, in part, the liver enzyme indicators of host response (Raadsma *et al*. 2008b). Since the Indonesian Thin Tail breed also displays partial resistance to *Haemonchus contortus*, and this resistance appears to be influenced by same gene, Raadsma (2009) has suggested that there may be a "broad effect" of the gene on immune response, because *Haemonchus* and *Fasciola* are from roundworm and flatworm genera, respectively.

It is also notable that GDH and GGT are important indicators of liver and bile duct injury in facial eczema disease in New Zealand (see later), although they are probably downstream indicators of injury, rather than part of the genetic cause of the injury in susceptible animals.

Flystrike and fleece-rot. These two diseases will be discussed together, because of the high genetic correlation (>0.9) between them (Raadsma, 1991). Fleece-rot is a precursor to flystrike. In Merinos, susceptibility to flystrike (body strike) is heritable (e.g., Raadsma 1991) reported an estimate of 0.26 ± 0.12). On the underlying scale, consisting of a continuous grading of liability, his data led to a heritability estimate of 0.54 ± 0.25. The review by Safari *et al*. (2005) reported heritabilities of 0.17 ± 0.02 for fleece-rot incidence, and 0.23 ± 0.02 for it as a severity score, in fine-wool Merinos. Slightly higher values were reported by McGuirk and Atkins (1984), and they also estimated a heritability of 0.40 ± 0.11 for fleece-rot liability on the underlying scale. The main fly species causing flystrike in Australia is *Lucilia cuprina*, and the last 15 years have seen its immigration and spread across New Zealand (Heath and Bishop 1995), leading to more intensive fly damage to New Zealand sheep. Mortimer *et al*. (2001) have published evidence suggesting that a major gene may account for 20% of the phenotypic variance in fleece-rot and 15% of the variance in body strike in Merinos, as a result of studies of selection lines of sheep bred for resistance or susceptibility to fleece-rot and flystrike. One alternative approach when wool is of very limited value is to select for bare rumps; Scobie *et al.* (2007) reported a heritability of 0.33 ± 0.06 for breech bareness score, and 0.59 ± 0.06 for the length of bare skin under the tail.

Lice. In a four-year study at AgResearch, infestations by the louse, *Bovicola ovis,* were monitored in Romney lambs managed primarily for other purposes at Wallaceville Station, Upper Hutt, New

Zealand (Pfeffer *et al*. 2007). This study included natural and artificial infestations, providing data for heritability estimates for log-transformed louse score of 0.22 ± 0.06 in autumn (~6 months of age), 0.34 ± 0.08 in winter, and 0.44 ± 0.09 for a combined score. Cockle scores from exposed lambs were also recorded *in vivo* on skin below a closely shorn area, and on pelts *post mortem*, and heritability estimates for cockle score were 0.06 ± 0.04, 0.45 ± 0.09 and 0.40 ± 0.09 in autumn, winter, and combined, respectively. The genetic correlation between mean louse score and mean cockle score was 0.97 ± 0.04, and the genetic correlations between mean louse score and the levels of two different anti-louse wool antigens were 0.96 ± 0.08 and 0.95 ± 0.09. It was concluded that monitoring wool antigens may be a practical way of producing an objective score of susceptibility to lice.

Mycotoxic diseases. Four mycotoxic diseases will be discussed: facial eczema (FE), caused by the sporidesmin toxin, ryegrass staggers (RGS), caused by the lolitrem B toxin from the *Neotyphodium lolii* endophyte, heat stress caused by ergovaline, and infertility caused by zearalenone. FE receives wide publicity in New Zealand, because of its prevalence in the North Island, but greater awareness of mycotoxins in both countries might assist farmers in trying to avoid grazing conditions where there is severe risk of mycotoxic poisoning of stock.

To protect against each disease, the options are 1). To avoid grazing toxin-containing pasture, 2). To protect animals that do graze it, or 3). To breed resistant animals. Recent reviews by Bishop and Morris (2007) and Morris and Phua (2009) have covered the genetics of resistance to these diseases. For sheep in New Zealand, the heritability estimate for FE resistance (via GGT as an enzyme indicator) is 0.45 ± 0.05 (Morris *et al*. 1995a), and for RGS (0-9 score) it is 0.36 ± 0.04 (Morris *et al.* 2007) with a previous estimate of 0.13 ± 0.05 from a binomial scoring system (Morris *et al.* 1995b). Relationships between the indicator for FE and the liver injury caused by the disease itself have been reported by Morris *et al.* (2002). Heritability estimates are not available for the susceptibility of sheep to ergovaline, but American data suggest that differences in animal susceptibility to tall fescue toxicosis (which is also caused by ergovaline) are heritable in cattle (Lipsey *et al.,* 1992), and experimental selection for or against resistance to dietary ergovaline was successful in mice (Hohenboken and Blodgett 1997). For zearalenone, urinary breakdown products of zearalenone have been measured after controlled dosing, and heritability estimates have been obtained in experimental animals (0.32 ± 0.10) and in the field (0.19 ± 0.07) (Amyes and Morris 2008).

A phenotyping service for FE susceptibility,'Ramguard', has been offered to New Zealand ram breeders since 1984 (Morris *et al*. 1994), and this provides a sporidesmin-dosing procedure and GGT-enzyme response measure, carried out under controlled conditions with veterinary supervision. According to the medium/high heritabilities reported for resistance to these mycotoxic diseases in sheep, it should be feasible to select for resistance in industry flocks, if there is a financial incentive. Breeding resistant rams might only be relevant to the objectives of farmers within a limited geographical range, but performance of commercial sheep farmed in that range is likely to improve markedly as a result. The next stage for FE is to offer a DNA marker test or marker-assisted selection, to breeders wishing to select for greater resistance. Experimental flocks have been generated and managed at AgResearch Ruakura for resistance or susceptibility to FE since 1975 (Morris *et al*. 1995a), and these have been used to study the underlying biology and to search for DNA markers of resistance (Phua *et al*. 2009). Genetic correlations between FE and production traits in the FE selection lines have been published: for resistant-line animals, lamb weights were, on average, 5-6% lighter, and yearling greasy fleece weights 8% heavier than in susceptible-line animals, and for reproduction there was no significant difference (Morris *et al*. 1999).

For RGS, a demonstration of the potential for widespread toxic effects has come from Reed *et*

al. (2005) who reported mass deaths in 2002 from severe "perennial ryegrass toxicosis" on 224 Southern Australian farms (29,109 sheep and 448 cattle; up to a 30% mortality is some grazing groups); 2002 was one of three severe seasons for this in a 20-year period in Southern Australia. The clinical symptoms for RGS in Southern Australia appeared more serious than those for RGS in New Zealand, and may have resulted from the Australian endophyte producing a combination of two toxins, lolitrem B and ergovaline (Reed *et al.* 2005). High positive correlations have also been reported in the USA between lolitrem B and ergovaline concentrations in over 450 endophyte-infected perennial ryegrass samples (Hovermale and Craig 2001). Divergent selection has been applied successfully since 1993 at Ruakura for resistance or susceptibility to RGS (Morris *et al*. 2007).

Indicative genetic associations are now available among effects of the various mycotoxic disease traits: a). a genetic correlation of 0.31 between resistance to FE and to RGS (Morris *et al*. 1995b), a positive relationship between resistance to lolitrem B and to ergovaline (unpublished material cited by Morris and Phua 2009), and c). a positive relationship between resistance to sporidesmin and ergovaline, in mice (Hohenboken *et al*. 2000). It is known that these toxins are from different chemical families, and that their modes of action are different. Nevertheless, finding positive associations suggests that at least some parts of the detoxification pathways are common. In the case of zearalenone, one of its breakdown products (α-zearalenol) is thought to be more oestrogenic than zearalenone itself, at least in monogastrics, where there is also competition with the host's oestrogen receptors (Hagler *et al*. 1979). There is a suggestion of an unfavourable correlation between resistance to FE and to zearalenone (Smith and Morris 2006), which could be explained by this finding.

Some other diseases

Mastitis. Bacterial infection in the mammary gland of most lactating ewes may not be as obvious a problem as in machine-milked cows, but it is a particular problem in dairy sheep operations. A brief review by Bishop and Morris (2007) reported that somatic cell counts (SCC) can be used as a diagnostic of subclinical infection in ewes as in cows (though this doesn't necessarily follow across species, e.g., in goats). Most recent estimates of heritability for SCC in ewes range from 0.10 to 0.20 (e.g., Gonzalo *et al*., 2003; Legarra and Ugarte, 2005), as in dairy cattle. The sign of genetic correlations between SCC and milk yield in dairy ewes is not clear, as a result of quite variable estimates published so far. Results of a search for QTL for mastitis and other lactation traits in dairy sheep have been summarised by Barillet (2007).

Footrot. Footrot is a bacterial disease caused by *Dichelobacter (Bacteroides) nodosus*, and it causes lameness in all classes of sheep. Raadsma *et al.* (1994) reported considerable genetic variation in levels of host resistance to both natural and artificial challenge, using a scoring system modified from one originally developed by Egerton and Roberts (1971). Given the moderate repeatability of footrot scores, combining data and estimating heritabilities from mean scores has led to heritability estimates "which approached 0.30 for most indicators" (Raadsma, 2000). Heritability estimates reported from Britain (Nieuwhof *et al*. 2008) were slightly smaller (0.12 to 0.23), and depended on incidence. In New Zealand, successful breeding programmes for footrot resistance have been reported for Corriedales by Skerman and Moorhouse (1987), and for Merinos by Patterson and Patterson (1989). Skerman *et al*. (1988) reported heritability estimates of 0.28 for a binomial index of footscald and/or footrot, and 0.17 for footrot incidence alone. Associations between resistance and the major histocompatibility locus have been observed (Escayg *et al*. 1997; Raadsma *et al*. 1999). A specific association with the DQA2 gene was reported by Hickford *et al*. (2004).

Pneumoni., Subclinical pneumonia is common in New Zealand amongst lambs under stress, and can be caused by viruses, bacteria or parasites (Merck Veterinary Manual 2009). It has been reported with an average flock prevalence of 22-29% in the Canterbury, Gisborne and Manawatu districts of New Zealand; prevalence was higher in northern New Zealand than in Southland (Goodwin-Ray 2006). There was a suspected breed difference (based only on anecdotal data), with the Merino being less susceptible than coarse-woolled breeds in matched environments. A farm-level survey by Goodwin-Ray *et al*. (2008) showed that management factors affecting incidence included shearing lambs on weaning day, breeding ewe replacements on the farm, increasing the percentage of lambs sold between March (~5 months of age) and May, whereas fixed stocking-rate grazing, and protective vitamin B12 injection at weaning were two factors associated with lower incidences. In Australia, Abbott and Maxwell (2002) noted: "It is likely that, either alone or in combination with other disease conditions, respiratory diseases are a significant cause of loss to the Australian sheep industry." These include parasitic and microbiological conditions. Although no genetic studies appear to have been published on pneumonia in sheep, Snowder *et al.* (2006) published data in the USA from cattle suggesting a heritable component of 0.18 for a respiratory disease score (transformed to the underlying continuous scale), and Heringstad *et al*. (2008) in Norway reported a heritability estimate of 0.05 (95% confidence intervals, 0.02 to 0.09) for respiratory disease incidence in cattle, using an underlying scale. It is possible that, in studies so far, the genetic variance is swamped by uncontrolled environmental variance, and that the latter could be reduced in more detailed future studies. By analogy, it has already been noted that heritability estimates of nematode parasite resistance are higher under experimental conditions than in field data (Morris *et al*. 1995c).

EXPERIMENTAL SELECTION FLOCKS

For those disease traits in New Zealand and Australian sheep where selection has been applied in experimental lines, genetic progress has indeed been achieved in each, with estimates of realised heritabilities from the 12 sets of actual selection lines averaging 0.28 (Morris 2000), with a range from 0.13 to 0.45 (only three below 0.20). The lines reviewed involved selection for one of six single traits: resistance to nematode parasites, resilience to nematode parasites, and resistance to facial eczema, ryegrass staggers, body strike, and dermatophilosis. Realised annual responses reviewed by Morris (2000) averaged 0.073 phenotypic standard deviations per year.

CONCLUSIONS

For the limited number of sheep diseases that could be reviewed here, most heritabilities ranged from 0.2 to 0.4. It can be concluded that genetic progress can be achieved if it is economic to apply selection pressure, and this prediction is borne out by experience from the experimental sheep selection lines described. Given the difficulty of scoring many of the diseases under field conditions, the advent of DNA marker technology could provide a large boost in the near future to reducing incidence of these diseases by breeding, in particular taking advantage of the high density single nucleotide polymorphism approach just coming on stream in sheep [http://www.agresearch.co.nz/snp/snp-chip.asp; accessed 7 June 2009]. Without this, the factors (apart from economics) determining feasibility of disease-resistance selection under commercial conditions are developing a scoring system with the required accuracy, and having the flock manager believe in the objectives sufficiently to disease-challenge animals, in spite of an expectation that this will reduce their own performance.

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