An update on genetic parameters for facial eczema susceptibility in New Zealand dairy cattle

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ABSTRACT

Resistance/tolerance to facial eczema (FE) is a heritable trait in New Zealand dairy cattle, as measured by genetic variation in liver enzyme levels. AgResearch has been collecting data from herds clinically affected by FE, by blood-sampling all cows in these herds, as a low cost method of phenotyping large numbers of animals. Over the past seven autumns, 66 herds and 14,799 cows were sampled. Breeding values for FE resistance were calculated for 238 sires. One complicating factor was the level of FE-protection provided by zinc sulphate administered through the farm water supply. Variable levels of serum zinc in cows were found, due to factors including water intakes and weather conditions. In zinc-treated herds there were three classes of cows: those still affected by FE, and others seemingly FE-tolerant either through genetics or having enough circulating zinc to provide protection. The zinc status of each herd was recorded at the time of blood sampling after a clinical outbreak. Data were analysed within zinc-treated and not zinc-treated herds to provide genetic parameters for each. Heritabilities in herds according to zinc status were very similar, regardless of zinc status.

Keywords: facial eczema; cattle; heritability; resistance; zinc.

INTRODUCTION

Facial eczema (FE) is caused by the toxin, sporidesmin. In susceptible cows, sporidesmin produced by spores of a fungus, *Pithomyces chartarum*, causes liver injury, with deleterious effects on milk production (Towers & Smith, 1978) and on survival in the herd (Steffert, 1970; Morris *et al*., 2002). The cost of FE to the dairy industry can amount to tens of millions of dollars (R.G. Jackson, Personal communication).

Dairy industry studies since 1989 have established that resistance to FE is inherited in cattle (Cullen *et al*., 2006), with a heritability of 0.40 ± 0.04 (standard error) across breeds and crosses. Since 2006, when the last paper was presented on this topic, collection of FE phenotypes has continued, by sampling cows, and in some cases, replacement calves and yearling heifers, in herds or mobs exposed to a severe enough challenge to have at least 3% clinical cases. Gamma-glutamyltransferase (GGT) levels were then measured from blood samples taken from all animals.

Zinc treatment, administered as zinc sulphate via the farm water supply, is also considered now; along with the effect that circulating zinc may have on an animal's resistance to FE. Recent studies at Ruakura (C.A. Morris, Unpublished data) have shown in cows, where zinc sulphate is the method of protection, that circulating zinc levels can be very variable across animals and also across time. The fact that more than half of the herds with clinical cases sampled in the past seven years have been using zinc sulphate supports this finding. It appears that the use of zinc in the sulphate form and at the concentrations used does not provide adequate protection to all animals in a herd, particularly in years with major challenge. In zinc-treated herds, there were cows still affected by FE, but also some seemingly tolerant cows which were either genetically tolerant to FE or had enough circulating zinc to provide protection. The zinc status of each herd was recorded at the time of blood sampling. Analyses presented here describe the genetic parameters over all cows, and within each zinc treatment group. The data collected from this work has led to the prediction of breeding values (BVs) for all animals, but particularly sires, for FE resistance.

MATERIALS AND METHODS

Animals

The current trial design generated data on much larger numbers of animals and their sires than is possible via artificial challenge, by using naturally challenged animals in dairy herds, located in the Waikato, Coromandel, Bay of Plenty and some in Taranaki. Herds were first identified in the autumn as having at least 3% clinical cases of FE. Within a herd, each grazing mob was reconstituted on paper to be as it was at the time of predicted exposure. For individual grazing mobs to be included in the genetic analyses, a threshold was set at 30% of animals having a GGT concentration in their plasma (Towers & Stratton, 1978) above the "reference" range. Absolute reference ranges differed between two commercial laboratories used because of their different methods of analysis. Blood samples for GGT analysis were then taken from all cows, including any dry cows, in each grazing mob in

TABLE 1: Summary of females from herds with pedigree data supplied, tested for resistance/susceptibility to facial eczema, by year and zinc status of herd.

Year	Zinc usage				Total cows
	Yes		No		
	Herds	Cows	Herds	Cows	
2004	1	278	2	540	818
2005	9	2,127	5	816	2,943
2006	6	1,199	4	1,016	2,215
2007	8	2,256	4	766	3,022
2008	6	1,468	6	1,259	2,727
2009	2	277	4	874	1,151
2010	4	1,049	5	874	1,923
Total	36	8,654	30	6,145	14,799

these herds, regardless of their individual clinical FE status. Pedigrees of cows were obtained from the herd-owner's records. The sampled cows generally had at least sire-pedigree known and some of these cows still had their dam in the herd, thus giving access to some maternal grand-sires. This was then sufficient to calculate BVs for the cows, and their sires via their progeny, within and across herds. Information from the herd-owner was obtained in order to define each cow's grazing group over the last three to four months during unintentional exposure to the FE-challenge. Herds were classified on the basis of their zinc usage, according to answers received by a brief interview on method(s) of protection used, and approximate starting dates.

Contemporary groups (grazing mob) which did not meet the 30% threshold for elevated GGTs were removed from the genetic analyses. Sixty-six dairy herds and 14,799 cows and replacements, sampled in the current trial since the autumn of 2004, met this criterion. Table 1 summarises the numbers of herds and cows sampled by their zinc status, across each of the last seven years. Data from all the previous trials in the years 1989 to 2004 (Cullen *et al.*, 2006) have been combined with this data for the present analyses, as the sires of animals in the current trial themselves had sires and grandsires in the previous trials.

Data analyses

As much pedigree information as possible was obtained on all animals and their sires, for inclusion in the analyses. There were up to 13 generations of pedigree information recorded on the paternal line, although much less on the maternal line. Cows recorded in herds routinely have their dam identified, in addition to their sire, and, where possible, the cow's grand-dam and maternal grand-sire may be recorded. Approximately 33% of all animals with data collected since 2004 have their maternal grand-sire identified.

TABLE 2: Parameter estimates ± standard error for three indicators of resistance to facial eczema; the enzymes gamma-glutamyltransferase (standardised log_eGGT), and glutamate dehydrogenase (standardised log_eGDH) and elevated GGT status above a threshold as a 0/1 score. Data were from affected contemporary groups, and on the basis of the zinc status of the contemporary group at the time of challenge (Non-zinc or Zinc). The parameters were: heritability (h^2 – the upper value on the diagonal – bold type), repeatability (the lower value on the diagonal), genetic correlation (below the diagonal) and phenotypic correlation (above the diagonal). Std = Standardised.

Status	Variate	Std log_eGGT	Std log_eGDH	Elevated GGT 0/1
All cows	Std log_eGGT	**0.34 ± 0.02** 0.82 ± 0.004	0.83 ± 0.01	0.77 ± 0.003
	Std log_eGDH	0.92 ± 0.03	**0.30 ± 0.04** 0.67 ± 0.01	0.68 ± 0.01
	Elevated GGT 0/1	0.98 ± 0.01	0.87 ± 0.04	**0.24 ± 0.02** 0.60 ± 0.01
Non-zinc treated	Std log_eGGT	**0.37 ± 0.03** 0.86 ± 0.004	0.83 ± 0.01	0.76 ± 0.005
	Std log_eGDH	0.93 ± 0.03	**0.33 ± 0.05** 0.70 ± 0.01	0.67 ± 0.01
	Elevated GGT 0/1	0.98 ± 0.01	0.85 ± 0.04	**0.26 ± 0.03** 0.63 ± 0.01
Zinc treated	Std log_eGGT	**0.33 ± 0.03** 0.67 ± 0.02		0.77 ± 0.005
	Elevated GGT 0/1	0.96 ± 0.01		**0.25 ± 0.03** 0.47 ± 0.03

The three traits analysed included; (i) GGT concentration, transformed on the natural logarithmic scale; (ii) GGT reported as a 0 or 1 score, indicating whether an animal had a GGT level within or above the normal (reference) range, and (iii) glutamate dehydrogenase (GDH) concentration, which is a second liver enzyme affected by FE, that was also transformed on the natural logarithmic scale. As a result of the herd means varying widely and distributions of the log values not giving an approximately normal distribution, the $\log_e$GGT and $\log_e$GDH data were standardised within every contemporary group before inclusion in the analyses. This was expected to reduce any effects of varying levels of FE challenge, and thus reduce some of the between-herd variation in GGT levels.

The full statistical model included a contemporary group defined as herd-year-grazing mob. Cow age was tested both as a fixed effect and as a covariate but only accounted for about 2% of the variation and was omitted from the final model. Animal-model restricted maximum likelihood analyses were then used in ASReml (Gilmour et *al.*, 2009), to estimate heritabilities, genetic correlations and BVs for these three traits, with a multivariate repeated-record model. Analyses were run across all current and historical data and then restricted to subsets of data based on zinc usage.

RESULTS

Table 2 shows the population parameters over all herds, and separately for non-zinc and zinc-treated herds, only including cows from affected contemporary groups. Overall, heritability estimates ± standard error for the standardised traits were 0.34 ± 0.02 for $\log_e$GGT and 0.30 ± 0.04 for $\log_e$GDH, with a genetic correlation of 0.92 ± 0.03 between them. The repeatabilities overall were 0.82 ± 0.004 for standardised $\log_e$GGT and 0.67 ± 0.01 for standardised $\log_e$GDH. The elevated GGT (0/1) score had a heritability of 0.24 ± 0.02 with a repeatability of 0.60 ± 0.01. Two hundred and thirty-eight sires had reliabilities of at least 0.60 for BVs for standardised $\log_e$GGT.

The genetic parameters were very consistent between the zinc and non-zinc datasets. The heritabilities were higher, but not at a statistically significant level (P = 0.9), in the non-zinc dataset. The zinc dataset is based entirely on data from herds blood-sampled since 2004 where one blood sample was collected per animal for GGT in a season, and GDH levels were not analysed in addition. Hence there are no parameters quoted for GDH in the zinc dataset. Some zinc-treated herds were sampled again in subsequent years providing across-year GGT data for cows, with an across-year repeatability in Table 2 of 0.67 ± 0.02. In contrast, the repeatability for both $\log_e$GGT (0.86 ± 0.004) and $\log_e$GDH (0.70 ± 0.01) in the non-zinc data is on a within-year basis where some animals have been serially blood-sampled after an artificial challenge. The overall repeatabilities quoted above are a combination of within- and across-year values.

DISCUSSION

The overall heritability and repeatability estimates reported here have reduced slightly from those reported by Cullen *et al.* (2006). This may be due to higher levels of pedigree errors in dairy herds, compared to the bulk of the earlier data which came from tightly-controlled trials. There were large differences among the GGT BVs of the proven sires and the overall range of standardised BV ($\log_e$GGT) for all sires with accurate proofs was 2.8 standard deviations. The heritability and the level of genetic variation are such that genetic progress would be made if selection was applied to reduce FE susceptibility, as has also been reported in studies with experimental sheep (Morris *et al.*, 1995).

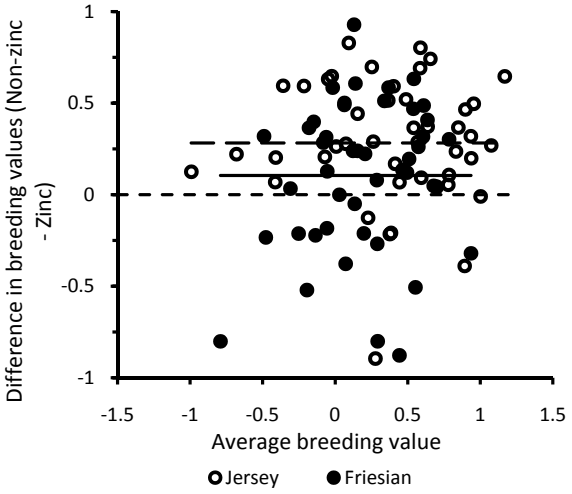
Our results here, and those reported by Cullen *et al*. (2006), have shown repeatedly that the heritability of $\log_e$GDH is smaller than that for $\log_e$GGT, under the conditions described. This is consistent with GDH being expressed earlier, peaking earlier and declining earlier, than GGT (Morris *et al*., 1998).

The heritability for the elevated GGT (0/1) score of 0.24 ± 0.02 is very high for a binary trait and compares favourably with heritabilities reported by Spelman *et al.* (2000), where Livestock Improvement Corporation (LIC) surveyed participating farmers in their sire proving scheme

TABLE 3: Summary of breeding values (BV) for standardised $\log_e$GGT for Friesian and Jersey sires in non-zinc and zinc herds, where the reliability of both BVs was at least 0.6.

Breed	Number of sires	Mean breeding values			Standard error of difference	P value
		Non zinc	Zinc	Difference (Non zinc - Zinc)		
Friesian	44	0.24	0.13	0.11	0.06	0.10
Jersey	45	0.53	0.25	0.28	0.05	<0.001

FIGURE 1: Plot of the difference in breeding values from Non-zinc herds and Zinc herds versus their average for standardised log_eGGT, for Friesian and Jersey sires where the reliability of both BVs is at least 0.60. The dotted line indicates agreement between the two breeding values; the solid line shows the non-significant difference for Friesians (0.11 ± 0.06) and the dashed line shows the significant difference for Jerseys (0.28 ± 0.05).



who recorded the incidence of clinical FE in their herds. Cows and replacement animals were scored for the LIC study on a 5-point scale (1 = Not affected, through to 5 = Died due to FE). Heritability estimates of visible FE symptoms in this work ranged from 0.03 to 0.17. That survey was scoring observed physical and behavioural changes such as photosensitivity. Our observations are that there is a very poor relationship between GGT levels and clinical signs in animals (C.A. Morris, Unpublished data), because GGT is an index of liver/bile duct damage, whereas visible facial eczema is an index of photosensitivity.

The regressions of BV for the elevated GGT (0/1) score on year of birth of bull and on the bull's breeding worth (BW) were calculated, giving 0.0082 ± 0.0017 ($P < 0.0001$) per year, on year-of-birth, and 0.00065 ± 0.00015 ($P < 0.0001$) per $, on BW. Thus over 25 years, which would equate with bulls born between 1977 and 2002, the BV for the elevated GGT (0/1) score has increased by 0.0082 x 25 = 0.205 or 20.5%. This can be interpreted as a 20.5% increase in likely liver damage in the 25-year period. The regression on BW was equivalent to a 3.25% increase in the elevated GGT (0/1) score for each 50 points increase in BW. This now occurs about every five years. To interpret both of these regressions requires the assumption that FE protection methods used now are similar to those 25 years earlier, as any improvement in protection would reduce the impact of the positive regressions.

The overall sire BV estimates are based on data from all herds regardless of zinc status. The relationship between sire BVs calculated with zinc or non-zinc data is of interest. We have only included sires that have reliabilities greater than or equal to 0.60 for both BVs in this comparison. The data is summarised in Table 3 by breed. There were a total of 89 sires which met this criterion with 44 being Friesian and 45 being Jersey.

Initially correlations between the two BVs were investigated but it is inappropriate to use correlations to compare methods, in general. A high correlation does not automatically imply that there is good agreement between the two methods. Correlation measures the strength of a relation between two variables, not the agreement between them, and depends on the range of the true quantity in the sample. If this is wide, the correlation will be greater than if it is narrow. A better approach, described by Bland and Altman (1986), is to plot the difference of the two methods on their average (Figure 1). Means of the BVs along with tests of differences are given in Table 3. The BV from the non-zinc herds is 0.28 ± 0.05 higher ($P < 0.001$) than the BV from the zinc herds for Jersey sires, for reasons which are still under investigation, whereas the Friesian difference is non-significant ($P = 0.10$).

In phenotyping for FE resistance using GGT, there appear to be three classes of cows in zinc-treated herds: the "susceptible", and those seemingly FE-tolerant either through genetics or with sufficient FE-protection from circulating zinc. With the above constraints, cow BVs need to be calculated within zinc treatment type, and apparently low GGT cows will have their BV adjusted according to their sire's BV. In contrast, sire BVs themselves can probably still be calculated from all herds regardless of zinc status. This is because of a likely averaging effect across all daughters for each sire.

CONCLUSIONS

This study continues work in dairy cattle on the genetics of resistance to FE. The latest estimate of the overall heritability, using standardised log_eGGT, is 0.34 ± 0.02. Although large differences among the BVs of some widely-used industry sires were identified, it would be difficult to exploit the genetic potential of highly resistant sires as these sires are generally old and have inferior genetic worth for milk production by the time that enough daughters are available to produce accurate proofs for FE resistance. It is imperative that sires in use today, or about to be used, have their level of resistance determined; either by (i) performance-testing through challenging bulls with an artificial dose of sporidesmin, (ii) progeny-testing a small number of

their offspring by the same method or (iii) the use of genomic selection. This would supersede our current methods of ranking bulls and provide valuable information on the current generation of bulls. For regions of the country where FE is a major problem, and if any controls are placed upon the use of zinc prophylactics, the breeding option is the only long-term solution.

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