Genetics of Tolerance and Resistance to Nematode Infection in Sheep

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ABSTRACT: We studied genetics of tolerance and resistance to nematodes in 962 Blackface lambs. A bivariate analysis was performed where tolerance was modeled as genetic effect for slope of reaction norm of bodyweight (BW) on faecal egg count (FEC) and resistance as genetic effect on levels of IgA against larvae (IgA). We observed a negative genetic correlation between BW at low and high FEC suggesting that different sets of genes control BW at low and high FEC. We observed a positive genetic correlation between BW at zero FEC level and IgA indicating that animals with high BW at zero FEC have genetically higher IgA level. We observed a negative genetic correlation between IgA and the slope of the reaction norm indicating that genetically more resistant animals are genetically less tolerant and vice versa. These results provide insight into genetics of tolerance and resistance.

Keywords: Nematode infection; Sheep; Tolerance; Resistance; Genetics

Introduction

The evolution of drug resistant pathogens warns the need of consistent strategies to control infections in farm animals. One approach is to enhance defensive ability of animals on population level by genetic selection. Defensive ability of a host against infections has two mechanisms: resistance and tolerance. Resistance is the ability of a host to resist the invading pathogen by for example preventing the pathogen from entering the body or shortening the life cycle of the pathogen in the body and remove it. Resistance is usually measured as the change in pathogen burden of a host during a certain period of time. Tolerance is the ability of a host to keep up its performance despite the infection. Tolerance is usually measured as the reaction norm of performance on change in pathogen burden (Simms (2000); Kause (2011)). In many studies on host-pathogen interaction in animals genetics of resistance have extensively been explored (Bishop and Morris (2007); Stear et al. (2009); Rout et al. (2011)). The genetic aspects of tolerance and any possible trade-off between tolerance and resistance are not yet very well known.

A major problem in sheep agricultural industry is gastrointestinal infection in sheep caused by nematodes. Gastrointestinal nematode infections cause huge performance reduction in grazing sheep. In sheep industry, genetic improvement for resistance to nematode infection has been applied successfully (Williams et al. (2010); Bishop (2012)). Tolerance to nematode infection and its relation to resistance are yet unknown. Therefore the aim of our study was to measure the tolerance of sheep to nematode infection as the reaction norm of body weight on faecal egg count and the genetic correlation between resistance and tolerance to nematode infections.

Materials and Methods

Data. From a commercial flock of Scottish Blackface sheep 962 lambs from 38 rams and 492 ewes were studied. Lambs were born outside from 1992 to 1996 during the last 2 weeks of April and the first week of May. Lambs grazed on pasture and were continuously exposed to natural mixed nematode infections. Three traits of lambs were used: 1) bodyweight recorded at 5 month of age (BW), 2) faecal egg count measured at 5 month of age (FEC), 3) plasma IgA activity against 4th stage *T. circumcincta* larvae (IgA). The number of available records for each trait was as follows: 687 for BW, 675 for FEC, and 699 for IgA. Faecal egg count and IgA were log transformed prior to further analysis ($\ln(\text{trait}+1)$).

Bivariate analysis of tolerance and resistance to nematode infection. We studied the genetic correlation between tolerance and resistance to nematode infection using a bivariate model. Tolerance was modeled as the genetic effect for the slope of the reaction norm of BW on FEC and resistance was modeled as the genetic effect on the level of IgA:

$$\begin{bmatrix}\mathbf{y}_{\text{BW}}\\ \mathbf{y}_{\text{IgA}}\end{bmatrix}=\begin{bmatrix}\mathbf{X}_{\text{BW}} & \mathbf{0}\\ \mathbf{0} & \mathbf{X}_{\text{IgA}}\end{bmatrix}\begin{bmatrix}\mathbf{b}_{\text{BW}}\\ \mathbf{b}_{\text{IgA}}\end{bmatrix}+\begin{bmatrix}\mathbf{Z}_{\text{s}} & \mathbf{Z}_{\text{x}} & \mathbf{0}\\ \mathbf{0} & \mathbf{0} & \mathbf{Z}_{\text{IgA}}\end{bmatrix}\times\begin{bmatrix}\mathbf{a}_{\text{int}}\\ \mathbf{a}_{\text{sl}}\\ \mathbf{a}_{\text{IgA}}\end{bmatrix}+\begin{bmatrix}\mathbf{e}_{\text{BW}}\\ \mathbf{e}_{\text{IgA}}\end{bmatrix},$$

where $\mathbf{y}_{\text{BW}}$ and $\mathbf{y}_{\text{IgA}}$ are the vectors of records for BW and IgA; $\mathbf{X}_{\text{BW}}$ and $\mathbf{X}_{\text{IgA}}$ are the incidence matrices for fixed effects for BW and IgA; $\mathbf{b}_{\text{BW}}$ and $\mathbf{b}_{\text{IgA}}$ are the vectors of the fixed effects for BW and IgA, which were overall mean, sex of lambs, age of lambs, and year in which the lamb was born. For BW, FEC was also put as a covariate to account for the average effect of FEC on BW; $\mathbf{Z}_{\text{s}}$ is the incidence matrix for intercept of reaction norm, $\mathbf{Z}_{\text{x}}$ is the matrix with the environmental parameter FEC as a covariate for the sire effects for the slope of the reaction norms, and $\mathbf{Z}_{\text{IgA}}$ is the incidence matrix for sire effects for IgA; $\mathbf{a}_{\text{int}}$, $\mathbf{a}_{\text{sl}}$ and $\mathbf{a}_{\text{IgA}}$ are the vectors with the estimated sire effects for intercept, slope, and IgA, respectively, with

$$\begin{bmatrix}\mathbf{a}_{\text{int}}\\ \mathbf{a}_{\text{sl}}\\ \mathbf{a}_{\text{IgA}}\end{bmatrix}\sim N(\mathbf{0},\mathbf{G}\otimes\mathbf{A}),\text{ where}$$

$$\mathbf{G} = \begin{bmatrix} \sigma^2_{a_{int}} & \sigma_{a_{int}\, a_{sl}} & \sigma_{a_{int}\, a_{IgA}} \\ \sigma_{a_{int}\, a_{sl}} & \sigma^2_{a_{sl}} & \sigma_{a_{sl}\, a_{IgA}} \\ \sigma_{a_{int}\, a_{IgA}} & \sigma_{a_{sl}\, a_{IgA}} & \sigma^2_{a_{IgA}} \end{bmatrix},$$

where $\sigma^2_{a_{int}}$, $\sigma^2_{a_{sl}}$, and $\sigma^2_{a_{IgA}}$ are the sire variances for $\mathbf{a}_{\text{int}}$, $\mathbf{a}_{\text{sl}}$ and $\mathbf{a}_{\text{IgA}}$; **A** is the additive genetic or numerator relationship matrix; $\mathbf{e}_{\text{BW}}$ ($\mathbf{e}_{\text{IgA}}$) is the vector of residuals for BW (IgA). For BW we considered heterogeneity of residual variance. For that, we sorted the data based on FEC and put them in 3 groups of equal size. Similar approach was used by Calus et al. (2002). We calculated the genetic correlations between BW at zero FEC level and BWs at other FEC levels using the **G** matrix.

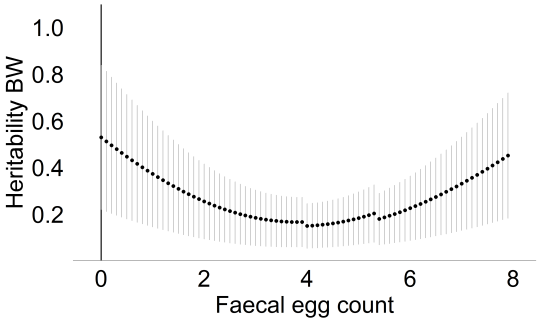

Figure 1. Heritability of body weight (BW) at different levels of faecal egg count (FEC) with heterogeneous residual variances. Note that FEC was transformed as log(FEC+1). Vertical lines show the ±se of the estimates. The breaks in the heritability graph are because of heterogeneous residual variances for three environments with low, medium, and high level of FEC.

Results and Discussion

Heritabilities of BW across different levels of FEC are in Figure 1. Heritabilities at low to high levels of FEC showed a parabolic shape. At zero level of FEC heritability was moderately high. Heritability dropped considerably at moderate levels of FEC. Heritability increased again by increasing the level of FEC. The change in the heritability of BW across different levels of FEC was due to change in genetic variance while environmental variance was rather stable across environments. Heritability of IgA was 0.59±0.20, which is in accordance with Davies et al. (2005). Genetic correlations between BW at zero FEC level and BWs at higher FEC levels are in Figure 2. The genetic correlations for BWs at low FEC levels were either one or close to one. The genetic correlation decreased when FEC levels increased. At very high levels of FEC the genetic correlation dropped to negative values. The negative genetic correlation between BWs in two extreme levels of FEC (zero and high FEC levels) indicates that lambs with high breeding values of BW at low FEC levels are the lambs with low breeding values of BW at high FEC levels and vice versa. The negative genetic correlation between BWs in two extreme levels of FEC also suggests that either two sets of genes are in charge of controlling BW in zero and high levels of FEC or the same set of genes have opposite effects in zero and high levels of FEC. Another indication for that two sets of genes are in charge of controlling BW at different levels of FEC is the parabolic shape of BW heritability at different levels of FEC. Because all animals are at pasture of the same farm, we can assume that animals are exposed to nematodes. Therefore, when FEC is low, BW is controlled mostly by genes in charge of resistance to nematode infection. When FEC is high, BW is controlled mostly by genes in charge of tolerance to nematode infection. The high heritability of BW at high levels of FEC, therefore, indicates that there is genetic variation among animals in tolerance to nematode infection. At medium levels of FEC, BW is controlled by both genes in charge of resistance and tolerance to nematode infection. The genetic correlations between IgA and intercept, and IgA and slope of the reaction norm for BW on FEC are shown in Table 1. There was a moderate positive genetic correlation between IgA and intercept. There was a moderately strong negative genetic correlation between IgA and slope. The positive genetic correlation between IgA and intercept indicates that lambs with higher BW at zero FEC levels have genetically a higher resistance to nematode infection. The negative genetic correlation between IgA and slope indicates that lambs with high IgA are genetically less tolerant to nematode infection. In other words, lambs that are genetically more resistant to nematode infections have genetically a lower tolerance to nematode infection.

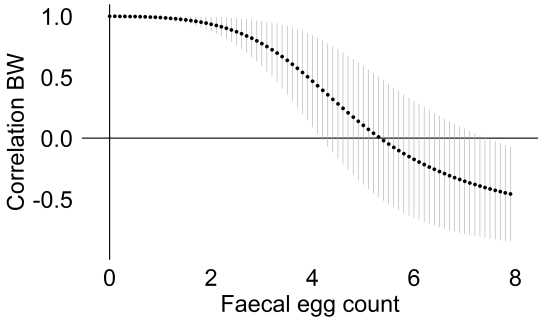

Figure 2. Correlation between body weight (BW) at zero faecal egg count (FEC) and body weight at any level of faecal egg count. Note that FEC was transformed as log(FEC+1). Vertical lines show the ±se of the estimates.

Table 1. Genetic correlations (se) between IgA and intercept and slope of the reaction norm of body weight on faecal egg count.

Resistance trait	Intercept	Slope
IgA[1]	0.48 (0.32)	-0.63 (0.25)

[1] Plasma IgA activity against 4th stage *T. circumcincta* larvae.

Conclusion

This study provides more insight into the genetics of resistance and tolerance to nematode infection. We showed that there is negative genetic correlation between resistance and tolerance. This implies that genetic improvement for either of the traits requires careful consideration of the other trait in selection decisions.

Acknowledgements

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Literature Cited

Bishop, S. C. (2012). Animal 6: 741-747.

Bishop, S. C., and Morris, C. A. (2007). Small Rumin. Res. 70: 48-59.

Calus, M. P., Groen, A. F., and de Jong, G. (2002). J. Dairy Sci. 85: 3115-3123.

Davies, G., Stear, M. J., and Bishop, S. C. (2005). Anim. Sci. 80: 143-150.

Kause, A. (2011). Genet. Res. 93: 291-302.

Rout, P. K., Chauhan, K. K., Matika, O. et al. (2011). Vet. Parasitol. 180: 315-322.

Simms, E. L. (2000). Evol. Ecol. 14: 563-570.

Stear, M. J., Boag, B., Cattadori, I. et al. (2009). Parasite Immunol. 31: 274-282.

Williams, A. R., Greeff, J. C., Vercoe, P. E. et al. (2010). Animal 4: 122-127.