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Prediction of prion protein genotype and association of this genotype with lamb performance traits of Suffolk sheep[1,2]

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ABSTRACT: The association of the prion protein (*PrP*) gene with susceptibility to scrapie has formed the basis of selection programs aimed at eradicating the disease from sheep populations. Animals are genotyped for the *PrP* gene and those with the less susceptible genotypes are selected. The objectives of this study were to determine the effectiveness of predicting PrP genotypes by using information from relatives and to investigate the association of the PrP genotype with lamb performance traits in Suffolk sheep. Data were obtained from a scrapie-affected flock maintained in Scotland. A total of 643 were animals genotyped at codon 171 of the *PrP* gene with 2 alleles, R and Q. The genotypes of these animals were used to predict the genotypes of 5,173 nongenotyped animals in the same flock using segregation analysis. The genotype of nongenotyped animals was predicted from the probabilities for each possible genotype; further, an overall index for each animal was calculated to reflect the accuracy of prediction. Association analyses of the *PrP* gene (using animals with both known and inferred genotypes) with BW at birth, at weaning (56 d), and at 150 d, and for backfat and muscle depths at 150 d of age were carried out. A linear mixed model with random direct and maternal additive genetic effects, maternal permanent and temporary environmental effects, and year of birth was tested, and the most appropriate model was used for each trait. The expected number of Q alleles carried (from 0 to 2) by each animal was calculated and used in the model as a linear and quadratic covariate to test for associations with possible additive and dominance *PrP* gene effects, respectively. Results showed that the genotypes of relatively few animals (235) were inferred with certainty (compared with the 5,173 nongenotyped animals). Approximately 25% of the 5,173 predicted genotypes were inferred with a genotype probability index of 50% and greater. There was no significant association of the *PrP* gene with any of the performance traits studied (there were no significant additive or dominance effects). Such was the case whether data on animals with known or with both known and predicted genotypes were considered. It can be concluded that selection for PrP-resistant alleles in Suffolk sheep is unlikely to affect performance directly.

Key words: gene association, genotype prediction, prion protein, scrapie, sheep

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INTRODUCTION

Susceptibility to classical scrapie, the transmissible spongiform encephalopathy of sheep, is associated with polymorphisms at codons 136, 154, and 171 of the prion protein (***PrP***) gene (Hunter et al., 1996). This association has been the basis of selection programs that form part of national scrapie eradication plans (e.g., Dawson and Del Rio Vilas, 2008). However, concerns have been raised regarding an antagonistic response in performance when selecting for scrapie-resistant alleles (e.g., Woolhouse et al., 2001; Sawalha et al., 2007a). Additionally, the eradication programs implemented in many countries rely on direct genotyping of potential

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breeding animals. However, inferring the genotypes of other relatives in the pedigree could save resources and accelerate the selection response for scrapie resistance.

Analyses of associations between the *PrP* gene and production traits have been conducted in several sheep breeds (Sweeney and Hanrahan, 2008). Most studies have provided little evidence to support an association between the *PrP* gene and production traits. However, the relationship of the *PrP* gene with performance of Suffolk sheep that show polymorphism for codon 171, but not for codons 136 or 154, has not been investigated using comprehensive statistical models. This study had 2 objectives: 1) to determine and evaluate the possibility of predicting the PrP genotype by using information from relatives, and 2) to investigate the association of the *PrP* gene with lamb growth performance traits in scrapie-affected Suffolk sheep.

MATERIALS AND METHODS

Animal Care and Use Committee approval was not obtained for this study because data were obtained from an existing database (Suffolk data at the Scottish Agricultural College).

Flock Management

Performance and PrP genotype data were recorded in a Suffolk sheep flock affected by scrapie and located at the Scottish Agricultural College. The flock was established in the early 1980s by purchasing approximately 160 mature ewes from approximately 50 pedigreed Suffolk flocks throughout Britain. The nonpregnant ewes were mated to either purchased or hired rams. Approximately 25 rams were used during this establishment phase. Pedigree information, tracing back to at least the sires and dams of each animal, was available on nearly all purchased animals (Simm et al., 2002).

In August of each year, ewes were exposed to rams for approximately 5 wk in single-sire groups. Ewes were housed indoors for 6 to 8 wk before lambing and received continuous supervision during the lambing period. Ewes with triplets, or those unable to rear twin lambs, had 1 or more of their lambs fostered to other ewes. Lambs were given ad libitum access to a creep feed from 7 d of age and, beginning at 42 d of age, were gradually changed to a pelleted high-energy (12.4 MJ of ME/kg of DM), high-protein (178 g of CP/kg of DM) performance test diet. Lambs were weaned abruptly at an average of 56 d of age and were then fed the performance test diet ad libitum until 150 d of age.

In 1985, the ewes were allocated to a selection or control line balanced by the source flock, age, BW, and BCS. Upon completion of the performance test period, within-line selection was carried out based on an index designed to increase the rate of lean deposition, with little change in the rate of fat deposition (Simm and Dingwall, 1989). Animals with the greatest index scores were selected as replacements within the selection line, whereas for the control line, animals with index scores closest to their family mean were selected as replacements. The flock also participated in a sire referencing scheme in which elite rams from member flocks were shared among all the flocks through AI. No animals sired by rams from the sire referencing scheme were retained as flock replacements.

During the 1992 and 1993 breeding seasons, 70 selection line ewes with greater index scores were superovulated and used as embryo donors as part of a wider study. Although embryos were transferred to crossbred recipients of either 50 or 75% Suffolk ancestry, management of the recipient ewes and embryo transfer lambs was identical to that of the rest of the flock.

Scrapie first appeared in the flock in November 1990 (Hunter et al., 1997). Thereafter, cases continued to occur and a total of 108 cases were detected until April 1999. The clinical signs included progressive loss of body condition and rubbing. Cases of scrapie were confirmed by histopathological detection of vacuolation of brain tissue.

PrP Genotyping

Prion protein genotypes, as determined by polymorphisms at codon 171, were obtained from DNA extracted from blood, tissue samples, or semen as described by Hunter et al. (1997). Genotypes were determined by PCR products, using methods described by Goldmann et al. (1996) and subsequent sequencing or oligonucleotide hybridization with allele-specific probes (Hunter et al., 1997). The alleles present at this codon code for 3 AA were arginine (**R**), glutamine (**Q**), and histadine (**H**). Genotypes found in the data set were RR, RQ, RH, QQ, and QH.

Genotyping protocols within the Scottish Agricultural College flock generally entailed genotyping of all animals that succumbed to scrapie as well as those that died, regardless of their scrapie status. Mass genotyping of performance-tested animals and previously retained ewes was also carried out when funding was available. There were 5,816 animals in the flock, of which 643 had PrP genotypes, as determined by polymorphisms at codon 171. No more animals could be genotyped because of restricted funds and blood samples available throughout the flock life. The distribution of animals by PrP genotype is shown in Table 1.

Prediction of the PrP Genotype of Nongenotyped Animals

Pedigree relationships among animals and the PrP genotypes from the 643 animals with a known RR, RQ, or QQ genotype were used to predict the genotypes of nongenotyped relatives by using segregation analysis with GENEPROB software (Kerr and Kinghorn, 1996). The inferred genotypes were represented as the probability of having the RR, RQ, and QQ genotypes. Each animal with an inferred genotype was also assigned a

Table 1. Frequency of prion protein genotype

Genotype[1]	Number	Frequency, %
RR	170	26.44
RQ	269	41.83
QQ	204	31.73

[1]R = arginine allele; Q = glutamine allele.

genotype probability index (**GPI**) to reflect the accuracy of genotype prediction as described by Kinghorn (1997). The GPI value ranged from 0% (if the animal had no relatives with known or predicted genotypes) to 100% [if the genotype was predicted with 100% certainty (e.g., both parents had homozygous genotypes)]. Genotype probabilities for animals with a GPI of 0% were excluded from the data set used to investigate the association of the *PrP* gene with performance traits.

Performance Data

Body weight was recorded at birth (**BWT**), weaning (**WWT**), and end of the performance test period (**WT150**). Animals were also ultrasonically scanned for backfat (**FD**) and muscle depth (**MD**) at the end of the performance test period. Performance data and PrP genotype (both known and inferred) were available, on 2,062 to 3,301 Suffolk lambs, depending on the trait analyzed (all records in all years were used in the study). The number of animals (lambs), sires, dams, dams with records, and litters (dam by year of lambing), and the mean and SD of different traits are presented in Table 2.

Statistical Model for the Association Analysis

The general form of the model tested was

$$\mathbf{y} = \mathbf{Xb} + \mathbf{Z_1a} + \mathbf{Z_2m} + \mathbf{Z_3r} + \mathbf{Z_4p} + \mathbf{Z_5t} + \mathbf{e},$$

where **y** is a vector of observations; **b** is a vector of fixed effects; **a** and **m** are vectors of random direct and maternal additive genetic effects, respectively; **r**, **p**, and **t** are vectors of random birth year, maternal permanent environmental, and maternal temporary environmental (litter) effects, respectively; **e** is a vector of random residuals; and **X** and $\mathbf{Z_1}$ to $\mathbf{Z_5}$ are incidence matrices relating observations to effects of interest. Birth year was fitted as a random effect rather than a fixed effect because of the relatively small number of observations in early birth years (Lewis et al., 2002).

The variance-covariance structures of the model fitted were $V(\mathbf{a}) = \mathbf{A}\sigma^2_a$, $V(\mathbf{m}) = \mathbf{A}\sigma^2_m$, $V(\mathbf{r}) = \mathbf{I_r}\sigma^2_r$, $V(\mathbf{p}) = \mathbf{I_p}\sigma^2_p$, $V(\mathbf{t}) = \mathbf{I_t}\sigma^2_t$, $V(\mathbf{e}) = \mathbf{I_e}\sigma^2_e$, and $\mathrm{Cov}(\mathbf{a},\mathbf{m}) = \mathbf{A}\sigma_{am}$, where **A** is the numerator relationship matrix, which was calculated using all pedigree data (n = 5,816), and $\mathbf{I_r}$, $\mathbf{I_p}$, $\mathbf{I_t}$, and $\mathbf{I_e}$ are the identity matrices of order equal to the number of levels of the corresponding effect (10 to 14 for birth years, 933 to 1,115 for dams, 1,459 to 1,942 for litters, and 2,062 to 3,301 for records). The symbols σ^2_a, σ^2_m, σ^2_r, σ^2_p, σ^2_t, and σ^2_e refer to the direct additive, maternal additive, birth year, maternal permanent environmental, maternal temporary environmental, and residual variances, respectively, and σ_{am} is the covariance between direct and maternal additive effects. All other covariances between random effects were assumed to be 0. Permanent and temporary environmental effects were attributed to the rearing dam in the priority of foster, embryo transfer surrogate, and then genetic dam. For BWT, where the presence of a foster dam was not relevant, the surrogate or the genetic dam was used.

The fixed effects considered to be included in the model were sex of lamb (intact male or female), type of birth (single, twin, and triplets or more) and rearing (single and twin or more), genetic line (selection, control, sire referencing, or foundation animals), age of birth or rearing dam (2, 3, 4, and 5 yr or greater), and breed of birth or rearing dam (100, 75, and 50% Suffolk). Linear covariates of date of birth for WWT, WT150, FD, and MD, and age at recording were also tested for significance. Only factors with significant effects ($P < 0.05$) were kept in the final model.

The random effects included in the model for a particular trait were selected by comparing log-likelihood values from a series of nested models. Improvement in model fit was assessed using the likelihood ratio test by comparing minus twice the difference in maximum log-likelihood value of tested models with a chi-squared

Table 2. Number of animals, sires, dams, dams with records, and litters and means and SD for different traits[1]

Trait	Animals	Sires	Dams[2]	Dams with records[2]	Litters	Mean	SD
BWT	3,301	158	880	751	1,786	4.60	1.04
WWT	2,813	157	836	709	1,638	23.0	4.56
WT150	2,062	137	700	288	1,242	63.3	8.48
FD	2,062	137	700	288	1,242	7.47	1.59
MD	2,062	137	700	288	1,242	30.1	2.60

[1]BWT = birth weight, kg; WWT = weaning weight at 56 d, kg; WT150 = 150-d BW, kg; FD and MD = fat and muscle depths at 150 d, mm.
[2]Genetic dams.

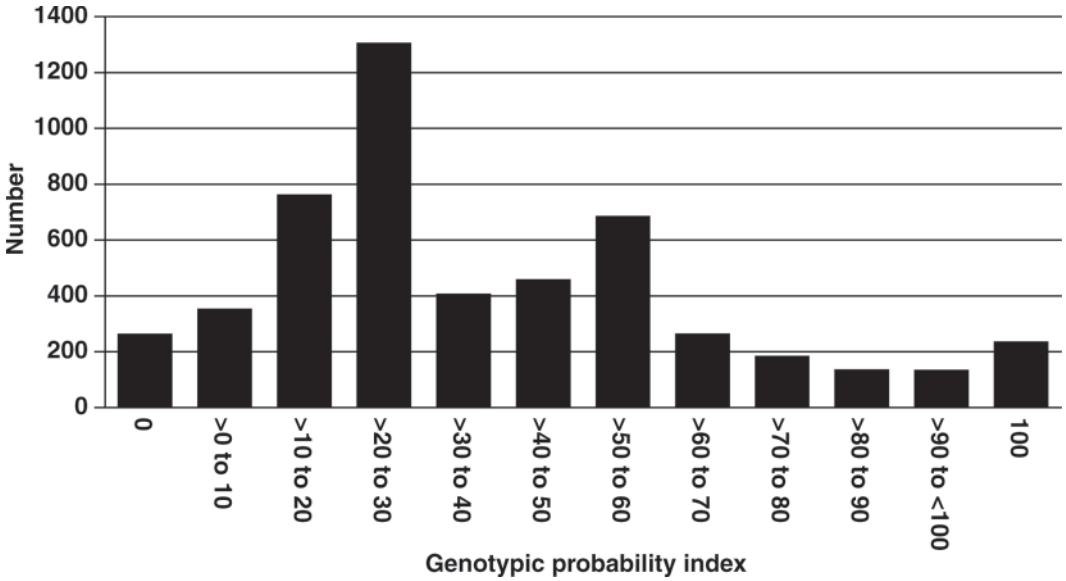

Figure 1. Distribution of predicted genotypes by the genotype probability index values.

distribution with appropriate degrees of freedom. The degrees of freedom were the differences in number of random effects between nested models. The data were analyzed with the ASReml Release 2.0 program (Gilmour et al., 2006).

Tests of Association

The association between *PrP* gene and performance traits was tested by fitting the expected number of Q alleles carried (0 to 2) as a linear and quadratic regression coefficient in the model. The expected number of Q alleles carried was calculated as twice the probability of having the QQ genotype plus the probability of having the RQ genotype. The probability of each genotype was predicted with GENEPROB for nongenotyped animals or was known for genotyped animals. The estimate of the slope of the linear regression line estimated the average or additive effect of gene substitution of the R by the Q allele. The dominance effect was tested by the significance of the fit of the quadratic term of the expected number of Q alleles carried.

RESULTS

Prediction of Genotype

Figure 1 shows the distribution of predicted records by their GPI value. The genotypes of 235 animals were inferred with certainty (GPI of 100%), which represents 35.5% more animals with unambiguous genotypes relative to the number of animals with known genotypes that were used for prediction (643 animals). Approximately 25% of the 5,173 predicted genotypes were inferred with a GPI of 50% or more. The predicted genotype of 262 animals had GPI of 0%.

Fixed Factors and Covariates

Table 3 shows the fixed factors that had a significant effect on different traits. Sex, type of birth or rearing, and age of the dam affected all traits ($P < 0.05$). Similarly, age at recording as a covariate (at weighing or scanning) was significant ($P < 0.05$) for all postnatal traits. Genetic line had a significant effect on all BW traits (BWT, WWT, and WT150), whereas the breed of birth or rearing dam affected ($P < 0.05$) BWT, WT150, and FD.

Random Effects and Estimates of Variance Components

The final model for all traits included random year of birth, and direct additive and maternal effects. The maternal permanent environmental effect was included in the model to analyze BWT and MD. Including a maternal temporary environmental effect (litter effect) significantly improved the fit of the model for BWT and WWT, and for FD.

Variance component and direct and maternal heritability estimates from the final model fitted are presented in Table 4. The estimate of direct heritability for BW traits increased as the age at measurement increased, with the least being 0.04 for BWT and the greatest being 0.28 for WT150. Conversely, estimates of maternal heritability for BW traits decreased with advancing age at measurement from 0.19 at birth to 0.10 at 150 d. Fat and muscle depths had larger estimates for direct heritability (0.40 and 0.31, respectively) and smaller estimates for maternal heritability (0.03 and 0.01, respectively) than the BW traits. The estimates of the covariance between direct and maternal genetic effects were not significant for any trait.

Table 3. *P*-values for fixed factors on different traits[1]

	Trait				
Factor	BWT	WWT	WT150	FD	MD
Sex	<0.01	<0.01	<0.01	<0.01	<0.01
Type of birth or rearing	<0.01	<0.01	<0.01	<0.01	<0.01
Genetic line	0.03	0.01	<0.01	NS[2]	NS
Age of dam	<0.01	<0.01	<0.01	<0.01	<0.01
Breed of dam	0.01	NS	<0.01	0.01	NS
Age at recording	NA[3]	<0.01	<0.01	<0.01	<0.01

[1]BWT = birth weight; WWT = weaning weight at 56 d; WT150 = 150-d BW; FD and MD = fat and muscle depths at 150 d, respectively.
[2]Not significant.
[3]Indicates not fitted in final model.

Tests of Association

Estimated means and SE by expected number of Q alleles carried are presented in Table 5 for different traits. There was no significant association between *PrP* gene and any of the traits studied. This was the case when testing both possible additive and dominance associations. There was a tendency for the Q allele to be associated with lighter BW and with smaller FD, but these differences were not statistically significant.

DISCUSSION

Results of the significance of fixed effects from this analysis are in general agreement with those of Simm et al. (2002), who analyzed the same traits from the same flock. Our direct heritability estimate for BWT was less than the average heritability estimates of BWT in meat sheep breeds, which were 0.15 using 6 studies and 0.12 using 7 studies (Fogarty, 1995; Safari et al., 2005). Estimates of direct heritability obtained in this study for the other traits were generally small, but still fell within the ranges of previously reported estimates, which ranged from 0.03 to 0.37 for WWT (Notter, 1998; Lewis and Beatson, 1999; Mousa et al., 1999), from 0.14 to 0.55 for later BW (Notter, 1998; Lewis and Beatson, 1999; Jones et al., 2004), and from 0.27 to 0.44 for FD and MD (Roden et al., 2003; Jones et al., 2004). Conversely, the maternal heritability estimates for BWT and WWT reported here were greater than those reported in the literature, where estimates ranged from 0.17 to 0.24 for BWT (Mousa et al., 1999) and from 0.04 to 0.15 for WWT (Notter, 1998; Lewis and Beatson, 1999).

The genotype of a few more animals relative to the number of animals with unknown genotype was predicted with certainty. However, the prediction of genotypes substantially increased the number of available records for evaluation of the association between PrP genotypes and performance in this study (because all predicted genotypes, regardless of level of certainty, were used in the study of association). The availability of a larger number of records reduces the error variance and increases the statistical power. To investigate this, the data were analyzed again but using only the genotyped animals and those whose genotypes were predicted with certainty. The numbers of records were 571 for BWT, 556 for WWT, and 515 for each of WT150, FD, and MD. The results from this analysis were in agreement with those from the previous analysis, which used all animals with known and inferred genotypes as described previously. However, the variances associated with the estimates of means were 51 to 79% smaller when using the larger data set with both known and

Table 4. Estimates and SE of variance components and heritability for different traits

	Variance component[2]					Heritability[3]		
Trait[1]	σ^2_r	σ^2_a	σ^2_m	σ^2_p	σ^2_t	h^2_a	h^2_m	h^2_{Total}
BWT	0.02 ± 0.01	0.03 ± 0.02	0.14 ± 0.03	0.09 ± 0.02	0.06 ± 0.02	0.04 ± 0.02	0.19 ± 0.03	0.14 ± 0.03
WWT	4.04 ± 1.82	2.25 ± 0.58	2.49 ± 0.46	NA[4]	2.02 ± 0.45	0.12 ± 0.03	0.13 ± 0.03	0.19 ± 0.03
WT150	6.37 ± 3.40	11.51 ± 2.30	4.18 ± 1.11	NA	NA	0.28 ± 0.05	0.10 ± 0.03	0.33 ± 0.05
FD	0.32 ± 0.16	1.00 ± 0.16	0.07 ± 0.05	NA	0.24 ± 0.07	0.40 ± 0.06	0.03 ± 0.02	0.42 ± 0.06
MD	1.11 ± 0.55	1.86 ± 0.31	0.06 ± 0.13	0.32 ± 0.14	NA	0.31 ± 0.05	0.01 ± 0.02	0.41 ± 0.05

[1]BWT = birth weight; WWT = weaning weight at 56 d; WT150 = 150-d BW; FD and MD = fat and muscle depths at 150 d, respectively.
[2]σ^2_r = birth year variance; σ^2_a = direct additive variance; σ^2_m = maternal additive variance; σ^2_p = maternal permanent environmental variance; σ^2_t = maternal temporary environmental variance.
[3]h^2_a = direct heritability; h^2_m = maternal heritability; h^2_{Total} = total heritability (which equals the sum of direct heritability and one-half of the maternal heritability).
[4]Indicates not fitted in final model.

Table 5. Least squares means and SE of different traits by expected number of glutamine (Q) alleles as predicted from the linear covariate[1]

Trait	Expected number of Q alleles			*P*-value additive[2]	*P*-value dominance[2,3]
	0	1	2		
BWT	4.45 ± 0.10	4.40 ± 0.10	4.35 ± 0.10	0.15	0.29
WWT	22.23 ± 0.68	22.04 ± 0.66	21.84 ± 0.69	0.25	0.36
WT150	60.92 ± 1.25	60.52 ± 1.22	60.13 ± 1.27	0.19	0.38
FD	7.75 ± 0.29	7.69 ± 0.28	7.62 ± 0.29	0.41	0.75
MD	29.47 ± 0.44	29.62 ± 0.43	29.78 ± 0.45	0.18	0.92

[1]BWT = birth weight, kg; WWT = weaning weight at 56 d, kg; WT150 = 150-d BW, kg; FD and MD = fat and muscle depths at 150 d, mm.

[2]Additive and dominance correspond to fitting Q alleles as linear and quadratic polynomial covariates in the model, respectively.

[3]Dominance effect was tested by the significance of the fit of the quadratic term of the expected number of Q alleles carried.

inferred genotypes compared with the smaller data set with only the certain genotypes for BWT, WT150, FD, and MD.

We found no significant association of PrP genotype with any of the traits analyzed. Selection against the scrapie-susceptible allele in Suffolk sheep (Q allele) is therefore expected to have no adverse effect on lamb growth traits. This is one of few studies to date that have tested and, where appropriate, fitted a maternal effects animal model when analyzing associations of PrP genotype with growth and body measures, and is the only study to date to do so when analyzing data from the Suffolk breed. Furthermore, results from this study are unique in that additive and dominance gene effects on performance have been tested, rather than all possible pair-wise comparisons among genotypes or comparisons with a single genotype (usually ARR/ARR).

Previous studies in various sheep breeds have found little or no evidence of association of the *PrP* gene with most lamb BW, backfat, and muscle traits (e.g., Alexander et al., 2005; Brandsma et al., 2005; Casellas et al., 2007). Sweeney and Hanrahan (2008) concluded that no negative associations exist between the *PrP* gene and lamb growth traits, based on their review of the relevant literature. A few studies have reported a significant association of the *PrP* gene with some lamb performance traits (De Vries et al., 2004; Tongue et al., 2006; Sawalha et al., 2007b). Nevertheless, the results from this research coincide with the predominant evidence of no association between the *PrP* gene and performance.

The data analyzed in this research came from a flock affected by scrapie, with animals exhibiting signs of scrapie genotyped for the *PrP* gene. Most of these animals had the QQ genotype (Hunter et al., 1997). Therefore, the lack of any significant difference in performance because of the PrP genotype might also be interpreted as no difference in the performance of scrapie-affected animals. However, that conclusion must be viewed with caution because not all QQ animals exhibited scrapie. Furthermore, the traits evaluated in this study were measured early in life (not more than 5 mo) before clinical signs of scrapie are often expressed.

When assessed, genotyped animals generally outperform nongenotyped animals within a particular population (Brandsma et al., 2004; De Vries et al., 2004, 2005; Moore et al., 2009), possibly because of breeders seeking to minimize genotyping costs by preselecting those animals to be genotyped based on performance measures (De Vries et al., 2005). Selective genotyping is known to have occurred within the flock analyzed in this study. Genotyping in this flock was based on performance and on clinical signs of scrapie in some years. All animals that exhibited signs of scrapie were preferentially genotyped, and 97% of these animals were of the QQ genotype. Therefore, the estimated frequency of the QQ genotype in this flock was substantially greater than previously reported estimates for Suffolk in the United Kingdom (Eglin et al., 2005). However, because preferential genotyping was based on expression of scrapie, which occurred in both the high-performing selection line and the average-performing control line, the genotyping bias based on performance was less of a problem in this flock compared with other commercial flocks. Additionally, the predicted PrP genotype, which was used in this study, allowed for the use of performance records of nongenotyped animals, which can also reduce the bias of selective genotyping. Therefore, the results from this study may be considered less liable to bias when compared with other studies investigating the association between the *PrP* gene and performance traits.

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