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Accuracy of genomic prediction within and across populations for nematode resistance and body weight traits in sheep

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Short title: Genomic predictions for sheep nematodes and weight

Abstract

Genomic prediction utilizes SNP chip data to predict animal genetic merit. It has the advantage of potentially capturing the effects of the majority of loci that contribute to genetic variation in a trait, even when the effects of the individual loci are very small. To implement genomic prediction, marker effects are estimated with a training set

including individuals with marker genotypes and trait phenotypes; subsequently genomic estimated breeding values (GEBV) for any genotyped individual in the population can be calculated using the estimated marker effects. In this study we aimed to: i) evaluate the potential of genomic prediction to predict GEBV for nematode resistance traits and body weight in sheep, within and across populations; ii) evaluate the accuracy of these predictions through within-population cross-validation; and iii) explore the impact of population structure on the accuracy of prediction. Four datasets comprising 752 lambs from a Scottish Blackface population, 2,371 from a Sarda x Lacaune backcross population, 1,000 from a Martinik Black-Belly x Romane backcross population, and 64 from a British Texel population were used in this study. Traits available for the analysis were faecal egg count for *Nematodirus* and *Strongyles* and body weight at different ages or as average effect, depending on the population. Moreover, immunoglobulin A was also available for the Scottish Blackface population. Results show that GEBV had moderate to good within-population predictive accuracy, whereas across-population predictions had accuracies close to zero. This can be explained by our finding that in most cases the accuracy estimates were mostly due to additive genetic relatedness between animals, rather than linkage disequilibrium (LD) between SNP and QTL. Our results, therefore, suggest that genomic prediction for nematode resistance and body weight may be of value in closely related animals, but that with the current SNP chip genomic predictions are unlikely to work across breeds.

Keywords: genomic prediction, population structure, nematode resistance, body weight, sheep

Implications

Genomic prediction utilizes SNP chip data to predict animal genetic merit. Using data from several populations, our results suggest that genomic prediction may be of value for nematode resistance and body weight in closely related animals, but with current technologies it is unlikely to work across populations. Genetic relatedness between animals and population structure affect these estimates and need to be taken into consideration before considering implementation.

Introduction

Traditional genetic improvement has relied on the use of phenotypes together with the knowledge of the pedigree of each animal to estimate its breeding value. This has led to genetic gains in most farmed species; especially with 'easy-to-measure' production traits. However, the efficiency decreases when traits are difficult to measure, have a low heritability, or cannot be quickly, inexpensively and correctly measured. An example is nematode resistance, assessed using indicator traits such as faecal egg count (FEC), which is critically important for the sheep industry.

To overcome this issue, there has long been an interest in using simply inherited genetic markers to increase the rate of genetic gain (Dekkers and Hospital, 2002). However, for many quantitative traits, such as production and health traits, a large number of loci appear to affect the trait, with each of them individually explaining only a limited proportion of the total genetic variance (Hayes and Goddard, 2001, Sanna *et al.*, 2008, Kemper *et al.*, 2011). Genomic selection (GS) has the advantage of potentially capturing the effects of the majority of loci that contribute to genetic variation, even when the effects of the individual loci are very small (Hayes *et al.*, 2009a). With GS, first marker effects are estimated with a training set (TS) which

includes individuals with marker genotypes and trait phenotypes; genomic estimated breeding values (GEBV) of any genotyped individual in the population can then be calculated using the estimated marker effects (Habier *et al.*, 2007). The resulting GEBV, therefore, exploit associations between markers and QTL through linkage disequilibrium (LD) and linkage, along with the capture of pedigree relationships between animals (Habier *et al.*, 2007).

Accessing sufficient animals to both train and validate GEBV remains challenging in practice, and cross-validation with individuals from the same population is often used to assess the accuracy of the GEBV (Habier *et al.*, 2007). However, validation studies can be also performed using separate phenotyped and genotyped populations (Hayes *et al.*, 2009a, Luan *et al.*, 2009, Su *et al.*, 2010), with an accuracy which depends on the genetic relationship of the validation set to the TS (Habier *et al.*, 2007, Habier *et al.*, 2010). This is possible because markers used in the statistical models to estimate marker effects also capture additive genetic relationships between individuals (Cockerham, 1969, Ritland, 1996), therefore, even if markers are not in LD with QTL, the accuracy of GEBV will still be non-zero. However, animals more closely related to those included in the TS are expected to obtain more reliable predictions (Habier *et al.*, 2007, Legarra *et al.*, 2008, Sonesson and Meuwissen, 2009).

At present, the accuracy of GEBV has been evaluated in experiments involving several livestock species, such as dairy (Harris *et al.*, 2008, Hayes *et al.*, 2009b) and beef (Saatchi *et al.*, 2011) cattle populations, chicken (González-Recio *et al.*, 2009), and sheep (Daetwyler *et al.*, 2010b, Daetwyler *et al.*, 2012a, Daetwyler *et al.*, 2012b, Duchemin *et al.*, 2012). Apart from the study of Kemper *et al.* (2011), the use of high density genomic information to select for nematode resistance in sheep has received

less attention. Therefore, the aims of this study were to: i) evaluate the potential of GS to predict GEBV for nematode resistance traits, as well as body weight, both within and across populations; ii) evaluate the accuracy of these predictions through within-population cross-validation; and iii) explore the impact of population structure within population, by decomposing the accuracy of genomic prediction into component parts.

Material and methods

Four datasets comprising 752 lambs from a Scottish Blackface (SBF) population, 2,371 ewes from a Sarda x Lacaune (SAR) backcross population, 1,000 lambs from a Martinik Black-Belly x Romane (MBR) backcross population, and 64 lambs from a British Texel (BT) population were used in this study. As shown in the principal components plot of the SNP chip markers reported in Supplementary Figure S1, the four populations are genetically distant. Genomic predictions were conducted firstly within population, using the SBF data. This was because of the availability of both pedigree and SNP marker data, along with several traits, allowing us to potentially explore a variety of trait architectures as well as contributions of LD and linkage to genomic predictions. Secondly, an evaluation of across-population prediction was conducted using all four populations, albeit with limited phenotypes common across datasets.

Phenotype data

SBF data: The SBF lambs were bred over a period of three years (2001-2003), with traits measured including lamb weights (16 and 24 weeks, and average animal effect from a repeatability model excluding pedigree) and faecal egg counts (FEC) for *Nematodirus* and *Strongyles* collected at 16, 20 and 24 weeks of age, and their

126 average animal effects as well as plasma IgA (on 737 out of the 752 lambs). The
127 population comprised F2 and double backcross lambs from two originally different
128 lines, bred from 10 sires (half-sib family size = 11-146). More details on the data
129 structure and the phenotypes are given in Riggio *et al.* (2013). Fecal samples were
130 collected from the rectum of each lamb at the time of weighing and used for FEC
131 assays, using the modified McMaster technique as described by Gordon and
132 Whitlock (1939) and Bairden (1991). The activity of plasma IgA against a somatic
133 extract of third-stage larvae from *Teladorsagia* was measured by indirect ELISA, as
134 described by Strain *et al.* (2002), using blood samples collected at 24 weeks of age.
135 The relative IgA activity was calculated according to the formula suggested by Sinski
136 *et al.* (1995). The average animal effects were estimated by fitting a repeatability
137 model to trait values across the different time points, and then standardized to a
138 mean of 0 and a standard deviation of 1. FEC and IgA measurements were all right-
139 skewed. Therefore, prior to analysis, FEC measurements were log-transformed by
140 *ln*(FEC+x), where x is a constant used to avoid the zero values, whereas IgA
141 measurements were cube-root transformed.

142 *Other populations:* Phenotypes available on BT lambs were for FEC at 20 weeks for
143 *Strongyles* and *Nematodirus*, and body weight at 24 weeks. A detailed description of
144 the data was given in Matika *et al.* (2011). The phenotype available for the two
145 remaining populations (SAR and MBR) was the “average animal effect” for
146 *Strongyles* FEC. A detail description of the animals in the MBR population was given
147 in Sallé *et al.* (2012), and for the SAR population in Sechi *et al.* (2009).

148 *Genotype data*

149 All animals from the four populations were genotyped using the 50k SNP chip. The
150 SNP genotypes data were subjected to quality control (QC) measures, specific for

each population (see Supplementary Material S1). After QC, 42,841 SNPs were available for the SBF and BT populations, 44,859 for the SAR, and 42,469 for the MBR. Out of these SNPs, 38,991 were in common among the four populations and therefore used for further analyses.

Assessment of GEBV predictive value

SBF data: For the analysis within population, validation sets were obtained by masking the phenotype (i.e., setting the phenotype as "unknown") for a defined number of individuals from the TS. The individuals whose phenotype was masked were selected in two different ways. The first way was through random selection: five non-overlapping cross-validation sets were created by randomly selecting 150 (152 for the fifth subset) lambs at a time, masking each phenotype only once. The second way was to select individuals belonging to specific families, to test the extent to which results differed depending on how related families were to the remaining families forming the TS.

Data were first analysed without fitting any polygenic or genomic effect, to correct for fixed effects. The following model was fitted:

$$y_{ijlmn} = \mu + S_i + K_j + L_l + G_m + A_n + \beta DB + e_{ijlmn}$$

where, y_{ijlmn} is the phenotype of the n^{th} individual, S_i is the effect of the sex (male and female), K_j is the effect of the year of birth (2001 to 2003), L_l is the effect of the litter size (single or multiple), G_m is the effect of management group (two levels, corresponding to those born in the first 2 weeks of the lambing season and those born subsequently), A_n is the effect of age of dam (1 to 4 years), DB is a covariate effect of day of birth and β its regression coefficient, and e_{ijlmn} is the residual error.

The resulting adjusted phenotypes or residuals (y*) were then analysed using the ASReml package (Gilmour *et al.*, 2009), fitting the model:

$$y^* = \mu + Zg + e,$$

where y* is a vector of the adjusted phenotypic records, **Z** is a design matrix, g is a vector of random additive genomic effects distributed as $N(0,\sigma_g^2\mathbf{G})$, σ_g^2 is the additive genetic variance, **G** is the genomic relationship matrix, and e is the vector of residuals. The **G** matrix was constructed using the method of VanRaden (2008). The genetic variance/covariance matrix and GEBV (i.e., $\hat{g}$) of the SBF lambs in the TS were estimated by utilizing both phenotype and genotype information. The predicted genomic breeding values (PGEBV), i.e. GEBV calculated without phenotypic information on the individual, were estimated fitting the model described above but masking the phenotypes of each subset in turn. Thus, in addition to its GEBV, after analysing each randomisation, every individual had a PGEBV obtained from marker data alone from random masking of phenotypes, with a similarly obtained PGEBV following masking of families.

Across populations: Two combined datasets were used for across population predictions, with SBF, SAR and MBR making the first set (4,123 individuals) and SBF and BT making the other (816 lambs). In the former data, two populations were used as TS to predict the third one (i.e., SAR and MBR to predict SBF; SBF and SAR to predict MBR; and SBF and MBR to predict SAR). Moreover, to test for the impact of cross-family links on GEBV, two analyses were conducted in which a few half-sib family members were allocated to the TS and used as a connection with the rest of the half-sib family members in the validation set. In these analyses, either one or 10

197 lambs from each half-sib family from the SBF data were randomly chosen to be in the
198 TS.

199 *Accuracy and predictive values of PGEBV*

200 Genomic prediction accuracies were calculated for each validation set (both within
201 and across populations). Firstly, the Pearson correlations of PGEBV with the
202 adjusted phenotypes ($r_{\hat{g}\hat{y}}$) were calculated and the accuracy ($r_{\hat{g}g}$) for each validation
203 set was estimated by dividing $r_{\hat{g}\hat{y}}$ by the the square root of the heritability of each trait
204 for that specific validation set:

205 $Accuracy = \frac{r_{\hat{g}\hat{y}}}{\sqrt{h_y^2}}$ (Legarra *et al.*, 2008).

206 The accuracy for each trait was then obtained by averaging the estimates across
207 validation groups.

208 The sampling properties of the prediction accuracies were explored by repeating the
209 overall within-SBF cross-validation analysis, described above, 10 times and
210 calculating the accuracy separately for each replicate. For each replicate, a new
211 randomisation was performed so that the individuals comprising each of the groups
212 were different. The standard error of the accuracy was then estimated as the
213 empirical standard deviation of the 10 accuracy values. This exercise was performed
214 for the average animal effect for *Strongyles* FEC, as an example trait.

215 Two further sets of analyses were performed using SBF data, alone. Firstly, we
216 calculated the correlation between GEBV and PGEBV. This case represents a
217 situation where progeny's performance is predicted from markers before the
218 availability of phenotypes. Secondly, the cross validation prediction accuracy analysis

was also performed using pedigree-based EBVs, rather than genomic EBVs. This addresses the question of how, in this population, the accuracy of genomic predictions compares to the accuracy of pedigree-based predictions.

Exploring contribution of population structure in the Scottish Blackface data

To explore the contribution of population structure to the accuracies of the genomic predictions, several analyses were performed. Firstly, to determine the effectiveness of the **G** matrix in capturing additive genetic effects relative to the **A** matrix, we analysed the SBF data fitting both the **G** matrix and the pedigree-based numerator relationship matrix **A** using the following model:

$$y^* = \mu + Zv + Zg + e,$$

where the effects are as defined above, with *v* being an additional vector of additive polygenic effects normally distributed as $N(0,\mathbf{A}\sigma_a^2)$, with **A** being the numerator relationship matrix.

Secondly, the contribution of population and genome structure to genomic prediction accuracies of the SBF population was assessed by fitting chromosome-specific **G** matrices. Following the methodology of Daetwyler *et al.* (2012a), 26 chromosome specific **G** matrices were calculated, using only the SNPs on each chromosome. Each chromosome was then fitted instead of the overall **G** matrix. To measure the proportion of the total genetic variance explained by each chromosome, we also carried out an analysis fitting each chromosome and the **G** matrix consisting of all SNPs minus those in that specific chromosome (which corresponds to fitting all chromosomes simultaneously). The following model was then fitted:

$$y^* = \mu + Zg_{chr} + Zg_{rest} + e,$$

where g_{ch} and g_{rest} are the vectors of additive genomic effects unique to the chromosome under investigation and to all remaining chromosomes, respectively. The terms g_{ch}, g_{rest} and e were assumed to be normally distributed: $N(0,\mathbf{G_{ch}}\sigma_{gch}^2)$ and $N(0,\mathbf{G_{rest}}\sigma_{grest}^2)$, respectively. Here, $\mathbf{G_{ch}}$ is the genomic matrix for one chromosome and $\mathbf{G_{rest}}$ is the genomic matrix estimated from the rest of the genome excluding the unique fitted chromosome markers.

Insight into the components contributing to the accuracy can be gained by regressing the difference in phenotypic variance explained by individually vs. simultaneously fitted chromosomal **G** matrices on chromosome length (Yang *et al.*, 2011, Daetwyler *et al.*, 2012a). This was given by this equation:

$$\sigma^2_{c(sep)} - \sigma^2_c = b_0 + b_1 L_c + e$$

where $\sigma^2_{c(sep)}$ is variance explained by each chromosome analysed individually and σ^2_c the variance when the chromosome are analysed jointly, with b_0 being the intercept which represents the component due to relatedness amongst animals rather than tagged QTL, and b_1 the slope that relates genetic variance to chromosome length (Lc), i.e. tagged QTL. We calculated the proportion of the genetic variance explained by the population structure (i.e. additive genetic relatedness as opposed to QTL tagged by the SNP chip) by dividing b_{0d} (intercept of the difference) with the intercept from regressing the variance explained by individually fitted chromosomes on chromosome length (b_{0i}).

Results

Accuracy and predictive values of PGEBV

265 *SBF data:* Correlations between PGEBV and adjusted phenotypes, with
266 corresponding accuracies for each trait, for the cross-validation groups in the SBF
267 population are reported in Table 1, together with the accuracies estimated using
268 pedigree-based EBV. Correlations varied between groups, ranging from marginally
269 negative (-0.027 in group 1 for *Nematodirus* FEC at 16 weeks) to positive and
270 moderate (0.382 in group 5 for IgA). Moderate accuracies $\left(r_{\hat{g}g}\right)$ were observed,
271 generally between 0.42 and 0.68, with the exception of the accuracy for *Nematodirus*
272 FEC at 16 weeks (0.10), this being the trait with the lowest heritability. Accuracies
273 using pedigree-based EBV ranged from 0.27 to 0.52, and were slightly lower than the
274 genomic EBV accuracies for 9 of the 12 traits. The empirical standard error of the
275 accuracy for *Strongyles* FEC average animal effect, estimated as the standard
276 deviation of the accuracies across the 10 replicated cross validation, was 0.04.
277 Correlations between GEBV and PGEBV (Table 2), representing the relationship
278 between genomic EBVs predicted with and without individual data were all strong
279 and positive. The average value across all traits was 0.76.

280 Lower correlation estimates between phenotype and PGEBV were obtained when all
281 members in one sire family were predicted from the remaining sire families in the
282 SBF data (Table 3). However, differences were observed in relationship connectivity
283 between families. For example, nematode resistance indicator trait results (i.e., both
284 IgA and FEC) showed that the families which were more closely related to the
285 remaining families in the TS were those with more accurate PGEBV. In particular, the
286 half-sib family sired by ram 22 (i.e., Fam22), which is the most highly related to the
287 remaining TS families (data not shown) showed the highest correlations. However,
288 different results were found for body weight, suggesting that not only relatedness is

important but other factors (such as trait heritability or markers in LD with mutations affecting the trait) may play a part.

Across populations: The correlations between PGEBV and adjusted phenotype for the *Strongyles* average animal effect were -0.054, -0.030 and 0.005 for SBF vs. (MBR plus SAR), MBR vs. (SBF plus SAR) and SAR vs. (SBF plus MBR) datasets, respectively. The correlations between PGEBV and adjusted phenotypes for the BT data vs. SBF were -0.012, -0.010 and 0.067 for *Strongyles* and *Nematodirus* FEC at 20 weeks and for body weight at 24 weeks, respectively. In both analyses, the predictions for genetically distant groups were usually close to zero. However, when one or 10 lambs from each sire family from the SBF data were randomly chosen and included in the TS, the correlations between PGEBV and y* were slightly higher, and always positive with 0.129 and 0.070 for SBF vs. (MBR plus SAR plus 10SBF) and SBF vs. (MBR plus SAR plus 100SBF), respectively.

Exploring contribution of population and genome structure

The results of the analysis in the SBF data, fitting either the **A** or **G** matrix alone, or both together, are reported in Supplementary Table S1. For some traits the heritability estimates were either completely explained by the **G** matrix (i.e., IgA and *Nematodirus* FEC at 20 weeks) or the **A** matrix (*Strongyles* FEC at 20 weeks and *Nematodirus* FEC at 16 weeks) when the analysis was done fitting both **G** and **A** matrices. However, for the other FEC traits (both *Strongyles* and *Nematodirus*) there was a contribution from both matrices. In general there was little discernible pattern in these results. Moreover, the relative partitioning of genetic variation between the **A** and **G** matrices may be expected to vary as the number and size of families varies, thus it is difficult to draw general conclusions from these results.

313 For the SBF population, heritability estimates were also obtained either fitting only
314 one chromosome or when simultaneously fitting one chromosome plus the whole **G**
315 matrix (results not shown). Although similar trends were observed, the proportions of
316 genetic variation accounted for when fitting only one chromosome were always
317 overestimated. However, in both cases it is possible to identify the chromosomes that
318 explain most of the genetic variation of the traits.

319 We tested the hypothesis that fitting all $\mathbf{G}_{ch}$ (i.e., chromosome-wide genomic
320 matrices) simultaneously would result in each chromosome explaining a fraction of
321 the total genetic variance proportional to its length, consistent with the polygenic
322 assumptions underlying GBLUP. Whilst there was a weak tendency for this to be the
323 case for most traits (as an example, Figure 1), the majority of the captured genetic
324 variation appeared to be independent of chromosome length. This can be seen in
325 Table 4 which reports intercept, slope, and R^2 for the three regressions (i.e., by fitting
326 each chromosome individually, by fitting all chromosomes simultaneously, and the
327 difference between the two) as well as the proportion of genetic variance explained
328 by relatedness for all traits considered. These proportions (ranging from 0.39 to 0.98,
329 with an average of 0.77) suggest that in most cases our accuracy estimates are
330 mostly due to additive genetic relatedness, rather than LD between SNP and QTL.
331 The **A**-matrix-derived heritabilities were compared to accuracies and proportion of
332 genetic variance explained by relatedness (b_{0d}/b_{0i}) for all nematode resistance
333 indicator traits (results not shown). Amongst the *Strongyles* FEC and IgA results
334 there was little discernible relationship between these variables. The *Nematodirus*
335 traits were more variable, however they tended to have lower heritabilities and
336 relatively large genetic effects (i.e. QTL) had previously been observed on some of

337 the smaller chromosomes (see Discussion) suggesting that the polygenic inheritance
338 assumption was inappropriate for the *Nematodirus* traits.
339
340 **Discussion**
341 One of the objectives of the current study was to understand the dynamics of
342 applying genomic selection to hard-to-measure traits using field data. We assumed
343 two scenarios, with the first scenario having young animals selected from markers
344 before their phenotypes can be measured and secondly, where we break the
345 assumption that the animals of the TS and the validation sets are from the same
346 population i.e., we explore situations where the animals vary from being closely
347 related to unrelated. Therefore, we explored the possibility of using genomic
348 predictions within and across populations; whilst prediction accuracies within a
349 population were good, with a small empirical standard error, our results highlighted
350 the difficulties of prediction using genetically distant individuals.

351 We also reported prediction accuracies estimated by using both the **G** and the **A**
352 relationship matrix. The accuracies estimated with the **G** matrix were usually higher
353 that those with the **A** matrix, suggesting an advantage in using genomic information
354 for predictions, even when pedigree knowledge is available. The one case where the
355 accuracies estimated with the **A** matrix was substantially better, *viz*. *Nematodirus*
356 FEC at 16 weeks, was for a trait for which heritability estimate was mostly explained
357 by the **A** matrix (Supplementary Table S1).

358 Although several studies on GEBV accuracy/reliability estimated from real data have
359 been reported in the literature for cattle with GEBV reliabilities ranging from 18 to
360 78% (Harris *et al.*, 2008, Hayes *et al.*, 2009b, VanRaden *et al.*, 2009), fewer are
361 reported for sheep. Our GEBV accuracies are similar to others obtained using a

362 medium-density markers chip of 15 to 79% for wool traits in Merino sheep (Daetwyler
363 *et al.*, 2010b), and 7 to 31% for carcass and meat quality traits in multi-breed sheep
364 data (Daetwyler *et al.*, 2012b). In a study on the Lacaune dairy sheep breed using
365 different genomic methods, Duchemin *et al.* (2012) reported accuracies varying from
366 0.4 to 0.6, according to the traits (i.e. milk yield, fat content, and somatic cell scores),
367 with minor differences among genomic approaches. These authors also showed that
368 the inclusion of molecular information, as compared with traditional schemes,
369 increased accuracies of EBV of young males at birth from 18 up to 25%, according to
370 the trait (Duchemin *et al.*, 2012). However, it has to be considered that the accuracy
371 of the GEBV depends on the size of the population and on the heritability of the trait.
372 For low heritability traits, a very large number of records will be required in the TS to
373 subsequently achieve high accuracies of GEBV in unphenotyped animals. If we
374 consider our SBF population, where the effective population size (Ne) is ~500 (Kijas
375 *et al.*, 2012), then according to the formula suggested by Daetwyler *et al.* (2010a) to
376 achieve an accuracy of 0.6, we would need ~ 30,000 individuals for a trait with very
377 low heritability (e.g., *Nematodirus* FEC at 16 weeks), and ~ 5,000 for a trait with
378 moderate heritability (e.g., IgA).

379 The current study explored the contributions of LD and relatedness to the accuracies
380 of genomic predictions. The heritability estimates obtained either fitting only one
381 chromosome or when simultaneously fitting one chromosome plus the whole **G**
382 matrix showed that nematode resistance in sheep is a complex trait with
383 contributions from many regions in the genome affecting these traits. However, with
384 the exception of *Nematodirus* FEC at 16 weeks (Supplementary Figure S2; Riggio *et*
385 *al.*, 2013), the results favour a polygenic mode of inheritance, which is largely
386 captured by additive relationships between animals. This is illustrated by the results

when a chromosome at a time was fitted, that overestimated the proportion of genetic variance explained as opposed to when one chromosome and the **G** matrix were simultaneously fitted. As highlighted by Daetwyler *et al.* (2012a), if the only contribution of the SNP to the accuracy of genomic prediction was through LD with QTL, and assuming a polygenic model, then a **G** matrix constructed from only the SNP on one chromosome should capture genetic variation in proportion to its length, assuming that there is no population stratification. However, this was not the case in our study. It was therefore clear that a large proportion of the accuracy of genomic prediction in the SBF population, at the current SNP density, is due to population structure, i.e. relatedness between animals. In other words, only a small proportion of the accuracy was due to LD between SNP and QTL.

This proposition was tested formally using the regression approach suggested by Yang *et al.* (2011). The intercept (b_{0d}) of the difference between the variance for each chromosome when analysed individually or simultaneously was highly significant for all traits ($P<0.0001$), with the exception of body weight at 24 weeks ($P=0.09$). On the other hand, the slope (b_{1d}) of the difference was significant only for some of the traits. These values show the importance of the relatedness in our SBF population, suggesting that most of our accuracy is probably captured by additive relatedness. The ratio b_{0d}/b_{0i} is a measure of the proportion of genetic variance explained by such relatedness (Yang *et al.*, 2011), and with the exception of NFEC16, this measure was high (0.59-0.98) and therefore accounted for most of the variation in our SBF GEBV predictions. Of interest is the observation that accuracy and the component due to relatedness were largely independent of the **A**-matrix-derived heritability estimates (results not shown).

411 The impact of relatedness has been previously studied, and differences in accuracies
412 have been ascribed to the number of relatives in the TS and the degree of additive-
413 genetic relationships with training individuals (Habier *et al.*, 2010). Legarra *et al.*
414 (2008) analysed accuracies of GEBV for individuals either related or unrelated to the
415 TS in a mouse population, concluding that markers were able to recover family
416 information to some extent. Our choice of predicting all members of a single sire
417 family from the remaining sire families in the SBF data was designed to reduce the
418 upward biases of accuracies resulting from within-family prediction when half-sib
419 families are randomly split between TS and validation sets. In this case we showed
420 that the closer the individuals in the validation set are to the TS, the higher the
421 accuracy. This is probably due in part to the fact that genomic predictions across
422 closely related individuals capture linkage effects, whereas those across distantly
423 related animals require LD between SNP and QTL. However, it should be noted that
424 although we used distinct sire families with the SBF data, these families were in most
425 part, also closely related.

426 We also estimated the accuracy achieved when predicting breeding values across
427 populations. These across-population accuracies were very low, sometimes even
428 negative. These low estimates may be explained by extension from our previous
429 results. Firstly, much of the accuracy in the SBF dataset was due to additive genetic
430 relationships between animals, as captured by the marker IBS relationships. This will
431 not be possible in distant populations. Secondly, the component of accuracy due to
432 LD between SNP and QTL is also likely to be low in distant breeds, as the linkage
433 phase between SNP and QTL will differ randomly in different breeds. The more
434 distant the relationship between individuals, the shorter the genomic distance over
435 which phase will be consistent. This outcome is reinforced by the finding that the

accuracy achieved for across-population prediction was somewhat higher when a small number of animals from the population to be predicted were included in the TS.

It has been suggested that the use of a different method (i.e., BayesSSVS; Verbyla *et al.*, 2009) could increase across-breed prediction, as it assigns SNP to either a distribution with very small variance (i.e. near 0) or one with a larger variance in the prediction model, unlike GBLUP which assumes that all SNP effects are sampled from distributions with the same variance (Daetwyler *et al.*, 2012a). However, this suggestion pre-supposes that the same gene variants are segregating in different populations, and that the SNP density is sufficient for there to be consistent LD between marker and QTL in (some of) the different populations. It has been suggested that the number of SNP needed to predict unrelated individuals is equal to 10NeL, where L is the length of the genome in Morgans (Meuwissen, 2009). In the SBF population, with Ne of ~500 (Kijas *et al.*, 2012) and L of approximately 27 Morgans, predictions for unrelated individuals would require at least 135,000 SNP. This marker density may be achievable with the forthcoming high density sheep SNP chip.

In summary, we have applied genomic prediction techniques to nematode resistance and body weight data and found GEBV which, at first sight, appeared to have moderate to good within-population predictive accuracy, despite a relatively limited training set. However, much of the accuracy achieved appears to be a result of the markers capturing additive genetic relationships between animals in the population. This is reinforced by the observations that (i) the accuracy tends to drop when predictions are across more distantly related animals in the same population, (ii) across-population predictions have accuracies close to zero and (iii) some across-population accuracy can be recovered by including a small number of animals from

the target population in the training set. These results suggest that genomic prediction for nematode resistance and body weight may be of value in closely related animals, but with the current SNP chip genomic predictions are unlikely to work across breeds.

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586 **Table 1** *Correlations between predicted genomic estimated breeding values and*
587 *adjusted phenotypes and accuracies* for the random cross-validation groups both*
588 *using the genomic relationship matrix and the pedigree-based relationship matrix in*
589 *the Scottish Blackface population*

	Group 1	Group 2	Group 3	Group 4	Group 5	Genomic-based accuracy	Pedigree-based accuracy
IgA	0.151	0.174	0.314	0.359	0.382	0.532	0.513
SFEC16	0.192	0.074	0.089	0.245	0.174	0.487	0.516
SFEC20	0.141	0.099	0.216	0.150	0.091	0.432	0.401
SFEC24	0.138	0.068	0.186	0.172	0.110	0.442	0.476
NFEC16	-0.027	0.059	0.071	0.034	-0.006	0.099	0.342
NFEC20	0.210	0.292	0.193	0.324	0.220	0.598	0.488
NFEC24	0.212	0.182	0.155	0.178	0.130	0.503	0.408
W16W	0.206	0.127	0.231	0.232	0.234	0.516	0.336
W24W	0.169	0.073	0.165	0.109	0.046	0.417	0.292
SFEC_av	0.319	0.179	0.254	0.303	0.175	0.540	0.442
NFEC_av	0.208	0.317	0.192	0.282	0.234	0.481	0.357
WW_av	0.149	0.147	0.195	0.136	0.057	0.684	0.270

590 IgA: Immunoglobulin-A; SFEC16, SFEC20, and SFEC24: faecal egg count at 16, 20 and 24 weeks for
591 *Strongyles*; NFEC16, NFEC20, NFEC24: faecal egg count at 16, 20 and 24 weeks for *Nematodirus*;
592 W16W and W24W: body weight at 16 and 24 weeks; SFEC_av, NFEC_av, WW_av: average animal
593 effect for *Strongyles* and *Nematodirus* faecal egg count and for body weight
594 *accuracy here is the average of the accuracies across validation sets, estimated as the correlation for
595 each validation set divided by the square root of its heritability
596
597

598 **Table 2** *Correlations between genomic estimated breeding values and predicted*
599 *estimated genomic breeding values for the random cross-validation groups in the*
600 *Scottish Blackface population*

	Group1	Group2	Group3	Group4	Group5	average
IgA	0.674	0.731	0.784	0.699	0.773	0.732
SFEC16	0.737	0.606	0.699	0.729	0.764	0.707
SFEC20	0.841	0.764	0.850	0.788	0.846	0.818
SFEC24	0.825	0.804	0.815	0.826	0.794	0.813
NFEC16	0.774	0.750	0.700	0.690	0.710	0.725
NFEC20	0.709	0.863	0.823	0.867	0.767	0.806
NFEC24	0.842	0.783	0.816	0.880	0.847	0.834
W16W	0.627	0.676	0.719	0.794	0.713	0.706
W24W	0.666	0.667	0.743	0.799	0.632	0.702
SFEC_av	0.811	0.697	0.777	0.769	0.795	0.770
NFEC_av	0.764	0.765	0.765	0.798	0.735	0.765
WW_av	0.661	0.779	0.828	0.830	0.750	0.770

601 IgA: Immunoglobulin-A; SFEC16, SFEC20, and SFEC24: faecal egg count at 16, 20 and 24 weeks for
602 *Strongyles*; NFEC16, NFEC20, NFEC24: faecal egg count at 16, 20 and 24 weeks for *Nematodirus*;
603 W16W and W24W: body weight at 16 and 24 weeks; SFEC_av, NFEC_av, WW_av: average animal
604 effect for *Strongyles* and *Nematodirus* faecal egg count and for body weight
605
606

607 **Table 3** *Correlations between predicted genomic estimated breeding values and*
608 *adjusted phenotypes for families in the Scottish Blackface population*

	Fam022	**Fam058**	**Fam085**	**Fam161**
IgA	0.324	0.087	0.174	0.119
SFEC16	0.198	0.023	0.179	0.055
NFEC16	0.108	-0.055	0.036	0.018
W16W	-0.072	0.162	0.291	0.124

609 IgA: Immunoglobulin-A; SFEC16, NFEC16, and W16W: *Strongyles* and *Nematodirus* faecal egg count
610 and body weight at 16 weeks
611

Table 4 *Intercept, slope (i.e., proportion of phenotypic variance/Mb), and R^2 for the three regressions (i.e., by fitting each chromosome individually, by fitting all chromosomes simultaneously, and the difference between the two) as well as the proportion of genetic variance explained by relatedness (b_{0d}/b_{0i}) for all traits considered*

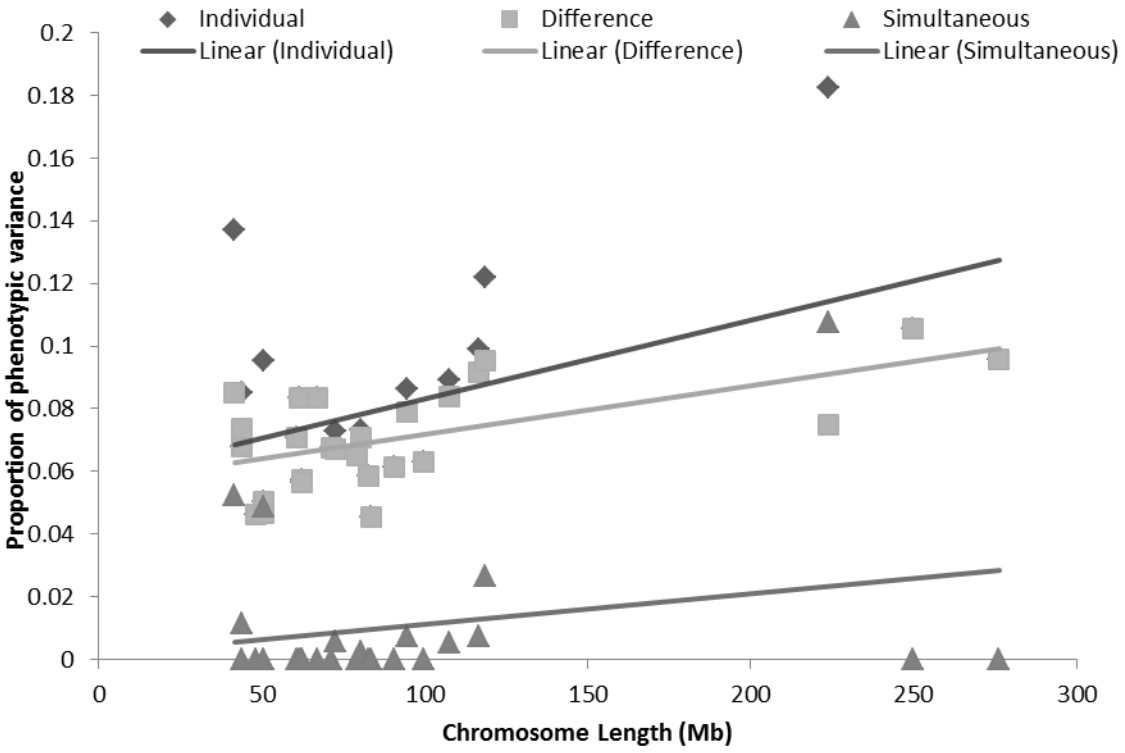
	Chromosome fitted individually			Chromosome fitted simultaneously			Difference			b_{0d}/b_{0i}
	R^2	Intercept	Slope	R^2	Intercept	Slope	R^2	Intercept	Slope	
IgA	0.26	0.058***	0.00025**	0.06	0.001	0.00010	0.34	0.056***	0.00015***	0.98
SFEC16	0.10	0.029**	0.00014	0.08	0.005	0.00011	0.02	0.024***	0.00003	0.84
SFEC20	0.10	0.041***	0.00009	0.00	0.012*	-0.00002	0.25	0.029***	0.00010**	0.71
SFEC24	0.06	0.039***	0.00006	0.02	0.008	0.00004	0.03	0.031***	0.00003	0.80
NFEC16	0.00	0.025**	-0.00002	0.00	0.015	-0.00002	0.00	0.010***	0.00000	0.39
NFEC20	0.44	0.063***	0.00020**	0.04	0.005	0.00005	0.56	0.058***	0.00015***	0.92
NFEC24	0.06	0.047***	0.00008	0.01	0.016*	-0.00003	0.28	0.032***	0.00011**	0.67
W16W	0.28	0.037***	0.00022**	0.00	0.009	-0.00001	0.46	0.028***	0.00024***	0.76
W24W	0.41	0.022***	0.00018***	0.00	0.009	-0.00001	0.28	0.013	0.00020**	0.59
SFECav	0.07	0.068***	0.00012	0.00	0.013	0.00001	0.17	0.056***	0.00011*	0.82
NFECav	0.07	0.079***	0.00015	0.02	0.011	0.00007	0.11	0.068***	0.00008	0.86
WWav	0.11	0.017**	0.00010	0.10	0.003	0.00008	0.01	0.015***	0.00002	0.85

IgA: Immunoglobulin-A; SFEC16, SFEC20, and SFEC24: faecal egg count at 16, 20 and 24 weeks for *Strongyles*; NFEC16, NFEC20, NFEC24: faecal egg count at 16, 20 and 24 weeks for *Nematodirus*; W16W and W24W: body weight at 16 and 24 weeks; SFEC_av, NFEC_av, WW_av: average animal effect for *Strongyles* and *Nematodirus* faecal egg count and for body weight

*P < 0.05; **P < 0.01; ***P < 0.001

620 **Figure 1** Proportion of phenotypic variance explained per chromosome for
621 Immunoglobulin-A (scattered points) and fitted regression (line). Chromosome fitted
622 individually (top regression) or simultaneously (bottom regression). Middle regression
623 results from plotting the difference between top and bottom regression.

624



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