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Genomic evaluation of binary traits in dairy cattle by considering genotype × environment interactions

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Abstract

Aim of study: To assess genotype by environment (G×E) interaction via single- and multi-trait animal models for binary traits in dairy cattle.

Area of study: University of Tabriz, Tabriz, Iran.

Material and methods: Phenotypic and genomic data were simulated considering a binary trait in four environments as different correlated traits. Heritabilities of 0.05, 0.10, 0.15, and 0.20 were considered to mimic the genetic variation of the binary trait in different environments. Eight scenarios resulted from combining the number of QTLs (60 or 300), LD level (high or low), and incidence of the binary trait (10% or 30%) were simulated to compare the accuracy of predictions. For all scenarios, 1667 markers per chromosome (depicting a 50K SNP chip) were randomly spaced over 30 chromosomes. Multi-trait animal models were applied to take account of G×E interaction and to predict the genomic breeding value in different environments. Prediction accuracies obtained from the single- and multi-trait animal models were compared.

Main results: In the models with G×E interaction, the largest accuracy of 0.401 was obtained in high LD scenario with 60 QTLs, and incidence of 30% for the fourth environment. The lowest accuracy of 0.190 was achieved in low LD scenario with 300 QTLs and incidence of 10% for the first environment.

Research highlights: Genomic selection with high prediction accuracy can be possible by considering the G×E interaction during the genetic improvement programs in dairy cattle.

Additional key words: accuracy of genomic prediction; simulation; genetic architecture; linkage disequilibrium; quantitative trait loci.

Abbreviations used: G×E (Genotype × Environment); GEBV (Genomic Estimated Breeding Value); HLD (High Linkage Disequilibrium); LD (Linkage Disequilibrium); LLD (Low Linkage Disequilibrium); QTL (Quantitative Trait Loci); SNP (Single Nucleotide Polymorphism); TBV (True Breeding Value).

Authors' contributions: All authors designed the study, read and approved the final manuscript. Analyzed the data: BE and MB. Wrote the paper: BE. Supervised the work: SAR, SA, and SK.

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Introduction

In the dairy cattle industry, phenotypic records of daughters from genotyped bulls are available in various climate conditions and countries because of the widely used artificial insemination. Such challenging environments might contribute to differential phenotypic expression across environments, which is known as the phenomenon of genotype by environment (G×E) interaction (Falconer & Mackay, 1996). Considering G×E interactions in genetic analyses can improve the genomic prediction of economically important traits (Tiezzi *et al.*, 2015), and neglecting interaction effects can result in a loss of genetic gain (Mulder & Bijma, 2005).

Multi-trait animal models were applied to quantify differences in gene expressions across different environments (Haile-Mariam *et al.*, 2015; Yao *et al.*, 2017; Bohlouli *et al.*, 2019). Researches on the multi-trait procedure are supposed to treat the performance of a genotype for a trait in different countries or regions as separate,

but potentially correlated traits (Hammami *et al.*, 2008; Santana *et al.*, 2012; Bohlouli *et al.*, 2014). Generally, in quantitative genetic studies, a large genetic correlation (>0.80) between the same trait evaluated in different environments indicates no evidence for remarkable G×E interaction (Robertson, 1959). In the last two decades, several studies have reported G×E interaction for milk production, fertility, and somatic cell score traits in dairy cattle. In some researches, the environment was measured as a continuous environmental descriptor, such as the temperature-humidity index (Brügemann *et al.*, 2011; Bohlouli *et al.*, 2013). However, in most of the researches, the environments were created as discrete scales, for instance, different regions (Santana *et al.*, 2012; Hamrouni *et al.*, 2014) and the herd production levels (Kolmodin *et al.*, 2002; Hammami *et al.*, 2009).

Genomic selection can improve genetic gain in dairy cattle by reducing generation intervals, increasing the accuracy of genomic prediction, and early selection (König *et al.*, 2009; Schefers & Weigel, 2012). The accuracy of genomic predictions strongly depends on several factors and parameters related to the genetic architecture of the trait of interest. The main factors are reference population size (VanRaden & Sullivan, 2010), the trait heritability (Goddard, 2009), markers density (Meuwissen, 2009), number of quantitative trait loci (QTLs) (Daetwyler *et al.*, 2008), distributions of allele frequencies (Clark *et al.*, 2011), levels of linkage disequilibrium (LD) (Yin *et al.*, 2014), genetic correlation between traits (Hayes *et al.*, 2009a; Calus *et al.*, 2013) and pedigree structure (Farah *et al.*, 2018). The accuracies of various genomic models (single- and multi-trait models) in different scenarios have been reported by some researchers (Jiang *et al.*, 2015; Bohlouli *et al.*, 2017). It has been indicated that the accuracy of genomic prediction for milk production traits via a multi-trait model was larger than that from a single-trait model (Guo *et al.*, 2014; Karaman *et al.*, 2018). Jiang *et al.* (2015) showed that accuracies of genomic prediction were higher for a multi-trait model than for a single-trait model, and increased with the increasing heritability of the trait and LD level.

In genomic selection, data simulations permit the researcher to survey the genetic architecture of the trait, the number of markers used for analysis, and the level of genetic relationships between the training and validation sets. Subsequently, genomic simulations suggest the possibility of evaluating different sources of variation in a population like drift, which cannot be assessed with most of the real data (Daetwyler *et al.*, 2013). Most simulation studies have focused on continuous traits in dairy cattle (Scheper *et al.*, 2016; de Oliveira *et al.*, 2019) and a few studies have considered G×E interactions for binary traits such as calving ease, survival, reproductive disorders, and disease resistance in dairy cattle. These traits are generally categorical, which are affected by more than one gene. In addition, such traits can show substantial G×E interactions (Naderi *et al.*, 2016). Carlén *et al.* (2006) demonstrated that the impact of G×E interactions on binary traits such as disease traits must be considered in genetic-statistical models. Therefore, the objectives of this study were (1) to simulate binary traits with different phenotypic expressions across environments, (2) to compare the accuracy of genomic predictions using single- and multi-trait animal models, and (3) to assess the predictive ability of the models for cows with and without phenotypic records in different environments.

Material and methods

Simulation of scenarios without G×E interaction

The QMSim software (Sargolzaei & Schenkel, 2009) was used to simulate dairy cattle populations with genomic information. According to Bohlouli *et al.* (2017), two types of historical populations were simulated to produce low (LLD) or high (HLD) levels of linkage disequilibrium. To achieve the desired LLD between a QTL and the markers, a constant size of 4000 was considered over 1600 generations, and then the population size increased to 4040 in the next 20 generations. Afterward, the constant size of 4040 individuals was simulated until generation 1640. For HLD scenarios, we simulated a "bottleneck effect". For this purpose, a constant size of 2000 individuals was simulated for 2500 generations, then during 70 generations, the population size was decreased to 200 individuals. Afterward, the population size increased to 4040 in generation 2600, and the size of 4040 individuals remained constant till generation 2620.

In the last historical generation, 40 sires were selected as founders to create a plausible population structure to imitate artificial insemination in the dairy cattle population with many individuals but a small effective population size (Bohlouli *et al.*, 2017). In the next step, animals from the last generation of the historical population were used as founders in 10 recent generations for both HLD and LLD scenarios. The recent population was extended for 10 generations by a random mating design. Each mating produced one progeny with a 50% probability of being each sex. The replacement rates were 50% and 25% for sires and dams, respectively.

Bi-allelic single nucleotide polymorphism (SNP) markers were randomly spaced over 30 chromosomes. Each chromosome was 100 cM in length. Simulation of 1667 bi-allelic markers on each chromosome represented application with 50,010 (50K) SNP chips. The number of QTLs affecting the trait of interest was set at 2 or 10 on each chromosome, indicating 60 or 300 QTLs in the whole genome. The marker and QTL positions were randomly assigned on the chromosome, and equal allele frequencies

were considered for both of them. The QTL effects were generated based on a gamma distribution with a shape parameter of 0.4. The gamma distribution assumes that most QTLs have small effects, and a few QTLs have large effects. The number of QTL alleles per locus was 2, 3, or 4 and was randomly assigned. Both marker and QTL mutation rates were 2.5×10^{-5}, whereas recurrent mutation was allowed for markers only. The total value of additive genetic variance was assigned to the QTL, indicating that there were no polygenic effects. The entire set of parameters of the simulation process is summarized in Table 1.

Simulation of scenarios with G×E interaction

We selected common sires having recorded daughters in all environments to make the genetic connection among them. The QMSim outputs were modified by an R code written by Yin *et al.* (2014). In this step, genotypes of 2000 cows in the 10th recent generation (the last generation) were used in the analysis. They were progenies from 40 sires, with an average of 50 daughters for each sire, and the pedigree contained all animals in the 10 recent generations. To mimic the different gene expressions in different environments, 60 QTLs and 300 QTLs were randomly divided into 10 groups, with an even group size of 6 QTLs and 30 QTLs, respectively. QTLs in groups of 1 to 7, 2 to 8, 3 to 9, and 4 to 10 were assigned to environments 1, 2, 3, and 4, respectively. This simulation strategy could also create a genetic correlation between environments by overlapping QTL groups in the four environments. As dairy cows usually have records only in an environment (region, farm and, etc.), we assigned cows to only one environment. But the sires have daughters in

Table 1. Parameters of the simulation process.

Parameters	Low linkage disequilibrium	High linkage disequilibrium
Historical population		
No. of generations	1640	2620
No. of animals in the first generation	4040	2000
Bottleneck	No	Yes [1]
No. of animals in the last generation	4040	
Current population		
No. of generations	10	
No. of founder males	40	
No. of founder females	4000	
No. of offspring per mate	1	
Probability for sex of the offspring	0.5	
Selection and mating designs	Random	
Replacement ratio for males	50%	
Replacement ratio for females	25%	
Criteria for selection/culling	Age	
Genome		
No. of chromosomes	30	
Length of each chromosome (cM)	100	
No. of QTL per chromosome	2 or 10	
Effects of QTL alleles	Gamma (0.4)	
No. of QTL alleles	Random (2, 3, 4)	
No. of biallelic markers per chromosome	1667	
Maker and QTL mutation rate	2.5×10^{-5} (recurrent for markers)	
Maker and QTL allele frequencies	Equal	
Crossover interference (cM)	25	
Position of markers and QTL	Random	

[1] The population size decreased from 2000 to 200 during 70 generations (from generation 2500 to 2570) and was 200 from generation 2570 to 2580. Then, the population size increased from 200 to 4040 during 20 generations (from generations 2580 to 2600).

all environments. The true breeding value (TBV) of the animals in every environment was the sum of the QTL effects of each animal in the corresponding environments. Phenotypes were generated by adding residuals to the TBVs. Then, to produce a binary phenotype, 200 or 600 cows (*i.e.* depicting 10 or 30% incidence, respectively) with the lowest phenotypic values received code 1 and the remaining cows were received code 0.

The heritabilities were 0.05, 0.10, 0.15, and 0.20 for the trait of interest in environments 1, 2, 3, and 4, respectively. We assigned 2000 cows with phenotypic records into the four environments (*i.e.* 500 cows per environment). Sires had at least 10 daughters in each environment. Such relationships could make a genetic connection across environments. The variance of TBVs was assumed as the additive genetic variance. Genetic correlations were calculated using correlations of TBVs of cows from different environments. Heritabilities and average genetic correlations across four environments from 10 replicates are listed in Table 2 for HLD and LLD scenarios.

Quality control

Quality control was carried out using the preGSf90 program in the BLUPF90 family (Misztal *et al.*, 2015). Markers with a minor allele frequency (MAF) less than 0.01 were discarded. To test Hardy-Weinberg Equilibrium (HWE), SNP was excluded if the difference between observed and expected genotype frequencies was greater than 0.15.

Linkage disequilibrium

The statistics of LD between all marker pairs in the simulated scenarios were assessed by calculating the squared correlation coefficient (r^2) value between all pairs of markers according to Hill & Robertson (1968):

$$r^2 = \frac{D^2}{f(A)f(a)f(B)f(b)} \quad (1)$$

where D = f(AB)-f(A)f(B), and f(AB), f(A), f(a), f(B), f(b) are observed frequencies of haplotypes AB and of alleles A, a, B, b in the population, respectively.

The PLINK software (Purcell *et al.*, 2007) was used to estimate LD between all marker pairs of 2000 cows in the last generation.

Statistical analysis

To take account of G×E interaction, a multi-trait animal model was applied, assuming a trait in different environments as different, but genetically correlated traits (Hammami *et al.*, 2009; Bohlouli *et al.*, 2017). The model was as follows:

$$\begin{bmatrix} \boldsymbol{y_1} \\ \vdots \\ \boldsymbol{y_4} \end{bmatrix} = \begin{bmatrix} \mathbf{1_1} & \mathbf{0} & \mathbf{0} \\ \mathbf{0} & \ddots & \mathbf{0} \\ \mathbf{0} & \mathbf{0} & \mathbf{1_4} \end{bmatrix} \begin{bmatrix} \mu_1 \\ \vdots \\ \mu_4 \end{bmatrix} + \begin{bmatrix} \boldsymbol{Z_1} & \mathbf{0} & \mathbf{0} \\ \mathbf{0} & \ddots & \mathbf{0} \\ \mathbf{0} & \mathbf{0} & \boldsymbol{Z_4} \end{bmatrix} \begin{bmatrix} \boldsymbol{g_1} \\ \vdots \\ \boldsymbol{g_4} \end{bmatrix} + \begin{bmatrix} \boldsymbol{e_1} \\ \vdots \\ \boldsymbol{e_4} \end{bmatrix} \quad (2)$$

where $\mathbf{y_i}$ is record for the i^{th} trait (i is 1 to 4 for the same trait in four different environments), $\mathbf{1_i}$ is the vector of 1, μ_i is the mean for the i^{th} trait, $\mathbf{Z_i}$ is the design matrix that relates genomic breeding values with response variables ($\mathbf{g_i}$), $\mathbf{g_i}$ is the vector of genomic estimated breeding values GEBVs) of animals (cows with the phenotype and their relatives) in the i^{th} environment, and $\mathbf{e_i}$ is the vector of random residual effects. For the i^{th} trait with n phenotype records, the dimensions of $\mathbf{1_i}$ and $\mathbf{Z_i}$ are n × 1 and n × number of animals in the pedigree, respectively. The distributions are assumed to be $\boldsymbol{g_i} \sim N(0, \mathbf{H} \otimes \mathbf{T})$, $\boldsymbol{e_i} \sim N(0, \mathbf{I} \otimes \mathbf{R})$ where:

$$\mathbf{T} = \begin{bmatrix} \sigma^2_{g1} & \cdots & \sigma_{g14} \\ \vdots & \ddots & \vdots \\ \sigma_{g41} & \cdots & \sigma^2_{g4} \end{bmatrix} \text{ and } \mathbf{R} = \begin{bmatrix} \sigma^2_{e1} & \cdots & 0 \\ \vdots & \ddots & \vdots \\ 0 & \cdots & \sigma^2_{e4} \end{bmatrix} \quad (3)$$

In the single-step genomic best linear unbiased prediction (ssGBLUP) model as developed by Aguilar *et al.* (2010), matrix **H** combines the pedigree-based numerator relationship matrix (**A**) with the genomic relationship ma-

Table 2. Heritabilities (above and below bold rows in diagonal for HLD and LLD scenarios, respectively) and genetic correlations (above and below diagonal for HLD and LLD scenarios, respectively) between different environments (the values in parentheses show the standard deviations).

Environment	1	2	3	4
1	**0.04 (0.016)**	0.860	0.746	0.578
	0.04 (0.013)	(0.081)	(0.091)	(0.192)
2	0.880	**0.08 (0.023)**	0.884	0.732
	(0.042)	**0.09 (0.019)**	(0.089)	(0.168)
3	0.762	0.879	**0.16 (0.029)**	0.860
	(0.144)	(0.109)	**0.14 (0.025)**	(0.095)
4	0.601	0.705	0.814	**0.25 (0.031)**
	(0.154)	(0.147)	(0.120)	**0.23 (0.029)**

trix (**G**) to consider animals with and without genomic information simultaneously. The **T** and **R** are the (co)variance matrices of additive genetic effect and residual for the four traits, respectively. The inverse of **H** was expressed as:

$$\mathbf{H^{-1}} = \mathbf{A^{-1}} + \begin{bmatrix} \mathbf{0} & \mathbf{0} \\ \mathbf{0} & \mathbf{G^{-1}} - \mathbf{A_{22}^{-1}} \end{bmatrix} \quad (4)$$

The G matrix was constructed according to the approach of VanRaden (2008):

$$G^{*} = \frac{(\mathbf{M}-\mathbf{P})(\mathbf{M}-\mathbf{P})'}{2\sum_{j=1}^{m} p_j(1-p_j)} \quad (5)$$

where **M** is a matrix of marker alleles with dimensions of the total number of genotyped individuals by the total number of markers (m) and coded -1, 0, and 1 for the homozygote, heterozygote, and another homozygote, respectively, and **P** contain allele frequencies expressed as a difference from 0.5 and multiplied by 2, such that column i of **P** is $2(p_i\text{-}0.5)$.

The genomic matrix is positive semi-definite but can be singular when the number of loci is restricted, or two animals have identical genotypes across all markers. Also, it will be singular if the number of genotyped animals exceeds the number of markers (VanRaden, 2008). To avoid singularity problems and make invertible matrices, **G** was obtained as $\mathbf{G} = w\mathbf{G^*} + (1 - w)\mathbf{A_{22}}$, where w = 0.95, **G*** is a genomic matrix before weighting, and $\mathbf{A_{22}}$ matrix is sub-matrix of **A** for genotyped animals. The Bayesian approach was performed using the THRIGIBBS3F90 program (Misztal *et al.*, 2015) for the threshold distribution of data. For each analysis, a total of 100000 iterations were run, with the first 30000 iterations were discarded as burn-in. From the remaining 70000 iterations, every 50th iteration was considered for analysis of the posterior distribution.

Results obtained from the single- and multi-trait animal models were compared to each other. In the single-trait models, the phenotypic records from different environments were considered as a trait. In addition, one more fixed effect was included in the single-trait models, indicating the environment.

In this study, we performed 10 replicates for each scenario, and results were averaged across replicates to evaluate the models, and the ANOVA procedure was used to compare the means of different scenarios by the Duncan test at a significance level of 5% (p<0.05) in SAS software (SAS, 2004).

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Accuracy of genomic prediction

The correlation between TBV and GEBV estimated from the single- and multi-trait animal models was considered as the evaluation criterion. Two strategies were used to evaluate the accuracy of genomic prediction for genotyped cows without phenotype (validation set). It is necessary for practical breeding programs because all the animals do not have phenotype information for all traits. In the first strategy, complete information (genotypes and phenotypes) for 1500 animals in three environments was available as a training set, and phenotypes from 500 genotyped cows in the fourth environment were excluded (validation set). Then GEBVs for all 2000 animals were estimated via a three-trait model. In other words, three GEBVs were estimated for each animal in the validation set. Afterward, for the environment without phenotypic records, accuracies of genomic prediction were calculated using TBVs of 500 cows in the validation set and their GEBVs in the other three environments. In the second strategy, phenotypic records from 25, 50, or 75% of cows in the extreme environment (the first or the fourth environment) were randomly masked and were used as the validation set. The remaining cows (*i.e.* with phenotypic records in the respective extreme environment and the other three environments) were used as the training set. Then, the accuracies of genomic prediction were calculated. For the single-trait models, the accuracy of genomic prediction was the correlation between GEBV of animals in the validation set (*i.e.* only one GEBV per animal) and their TBV in a specific environment.

Hypothesis testing

To test for the effect of G×E interaction on the accuracy of genomic prediction in binary traits, the null and alternative hypotheses are simply given as: (H0): no gain in the accuracy of genomic prediction by considering G×E interaction in binary traits; (HA): gain is present in the accuracy of genomic prediction by considering G×E interaction in binary traits.

Results

Linkage disequilibrium

The average r^2 value across 10 replicates between SNP pairs for both the low LD and high LD scenarios with 50K SNP chip applications were plotted against a marker distance of up to 2 megabase pairs (Mbp) on the

first chromosome (Figure 1). The average r^2 for all scenarios decreased with an increase in marker distances. The average r^2 for HLD scenarios was larger than for the respective values for LLD scenarios, especially for a small distance between 2 SNPs. We found substantial declines in average r^2 for distances in the range from 0 to 0.8 Mb. But the declines were low to moderate for distances ranging between 0.8 and 2.0 Mb. When the distance between markers was larger than 5.0 Mb, no difference in r^2 was observed between HLD and LLD scenarios. The average r^2 was 0.005 when distances were 100 Mb.

Genomic prediction accuracies

A: Single-trait animal model

Accuracies of genomic prediction using eight scenarios (HLD or LLD; 60QTL or 300QTL; 10% or 30% incidence) obtained from the single-trait model are listed in Table 3. This model considers only animals in the environment that have phenotypic records. There are four TBVs and four GEBVs per cow. In general, the accuracies of prediction increased with increasing heritabilities. The accuracies of genomic prediction for the scenarios with HLD were significantly larger compared to those with LLD. Accordingly, the largest accuracies were achieved when the scenario with HLD, 300 QTLs, and 30% incidence (HLD_300QTL_0.3) was used. Generally, accuracies for scenarios with 30% incidence were significantly larger than those with 10% incidence (p<0.05). For LLD scenarios considering the incidence, there was no significant difference between the accuracies of scenarios with 60 QTLs and 300 QTLs. However, significant differences between the accuracies were observed when HLD scenarios were simulated. For instance, the accuracy obtained for the HLD_60QTL_0.1 scenario (0.143) was significantly (p<0.05) lower than that for the HLD_300QTL_0.1 scenario (0.210). The differences between accuracies for scenarios with 10% and 30% incidences were remarkable when heritability was high. For instance, the accuracies of genomic prediction were 0.102 and 0.145 for the scenario with low incidence (LLD_300QTL_0.1) and the accuracies were 0.135 and 0.200 for the scenario with high incidence (LLD_300QTL_0.3) when heritabilities were 0.05 and 0.20, respectively. In most cases, increasing the number of QTL from 60 to 300 had no significant effect on the accuracy of genomic prediction.

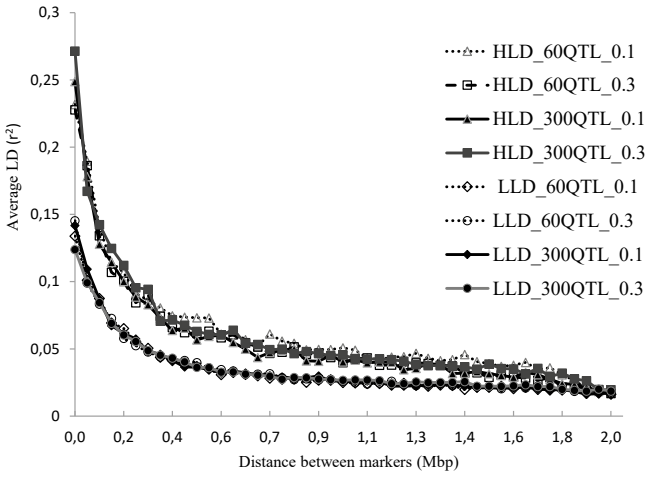

Figure 1. Average linkage disequilibrium (LD) measured by squared correlation coefficient (r^2) between SNP markers dependent on their marker distance for different scenarios. Scenarios consist of high or low linkage disequilibrium (HLD or LLD), different numbers of QTL (60QTL or 300QTL), and different incidences of the binary trait (10% or 30%).

B: Multiple-trait animal model

— **Cows with phenotypes.** The four-trait animal model was applied when considering the traits in four environments as four different traits and the accuracies of genomic predictions are presented in Table 3. For all scenarios and all environments, the accuracies obtained from the four-trait model were larger in comparison to the respective values obtained from the single-trait model (Table 3). Like the single-trait models, accuracies of genomic prediction increased with increasing heritabilities when using muti-trait models. The largest accuracy (0.401) was achieved in the fourth environment for the scenario HLD_60QTL_0.3. Accuracies for scenarios with HLD were non-significantly larger than those for scenarios with LLD. Prediction accuracies decreased non-significantly when using 300 QTLs instead of 60 QTLs. Generally, accuracies for scenarios with 30% incidence were significantly larger than those for 10% scenarios (p<0.05). For the first environment, no significant difference was found between the scenarios. The scenario with LLD, with 300 QTLs and with 10% incidence (LLD_300QTL_0.1) had the lowest accuracy across all environments.

— **Cows without phenotypes.** The accuracies of genomic predictions obtained from the three-trait animal models (Table S1 [suppl]) are lower than those obtained from the four-trait animal models (Table 3). The accuracies increased non-significantly when scenarios with HLD were used instead of the scenarios with LLD. In comparison to the accuracies for animals (*i.e.* as the validation set) in the extreme environments, the accuracies were larger when animals in the second or in the third environment were used as the validation set. There was no significant difference between the accuracies from scenarios with 60 and 300 QTLs. Generally, accuracies for the scenarios with 30% incidence were larger than those for 10% scenarios. Among all scenarios, higher prediction

Table 3. Accuracy of genomic predictions and standard deviations (in parenthesis) for animals in four environments using single- and four-trait animal models over different scenarios. Scenarios consist of high or low linkage disequilibrium (HLD or LLD), different numbers of QTL (60QTL or 300QTL), and different incidences of the binary trait (10% or 30%).

Scenarios	Model	Environment (Heritability)			
		1 (0.05)	2 (0.10)	3 (0.15)	4 (0.20)
HLD_60QTL_0.1	1	$0.117^{cd,A}$ (0.063)	$0.131^{b,A}$ (0.072)	$0.143^{c,A}$ (0.064)	$0.135^{d,A}$ (0.069)
	2	$0.252^{a,A}$ (0.164)	$0.270^{abc,A}$ (0.093)	$0.279^{bc,A}$ (0.091)	$0.286^{bc,A}$(0.097)
HLD_60QTL_0.3	1	$0.187^{ab,A}$ (0.074)	$0.208^{a,A}$ (0.043)	$0.226^{ab,A}$ (0.040)	$0.228^{ab,A}$ (0.069)
	2	$0.292^{a,B}$ (0.155)	$0.362^{a,AB}$ (0.075)	$0.372^{a,AB}$ (0.061)	$0.401^{a,A}$ (0.065)
HLD_300QTL_0.1	1	$0.184^{abc,A}$ (0.063)	$0.199^{a,A}$ (0.060)	$0.210^{ab,A}$ (0.048)	$0.162^{cd,A}$ (0.043)
	2	$0.238^{a,A}$ (0.100)	$0.246^{bc,A}$ (0.080)	$0.269^{bc,A}$ (0.106)	$0.273^{bc,A}$ (0.074)
HLD_300QTL_0.3	1	$0.208^{a,A}$ (0.079)	$0.245^{a,A}$ (0.071)	$0.262^{a,A}$ (0.067)	$0.243^{a,A}$ (0.059)
	2	$0.290^{a,A}$ (0.147)	$0.318^{ab,A}$ (0.126)	$0.348^{ab,A}$ (0.091)	$0.354^{ab,A}$ (0.098)
LLD_60QTL_0.1	1	$0.101^{d,A}$ (0.061)	$0.114^{b,A}$ (0.078)	$0.127^{c,A}$ (0.091)	$0.113^{d,A}$ (0.086)
	2	$0.197^{a,A}$ (0.181)	$0.206^{c,A}$ (0.090)	$0.232^{c,A}$ (0.088)	$0.239^{c,A}$ (0.075)
LLD_60QTL_0.3	1	$0.159^{abcd,B}$ (0.070)	$0.198^{a,AB}$ (0.063)	$0.220^{ab,A}$ (0.046)	$0.170^{bcd,AB}$ (0.044)
	2	$0.289^{a,A}$ (0.146)	$0.329^{ab,A}$ (0.096)	$0.370^{a,A}$ (0.049)	$0.383^{a,A}$ (0.079)
LLD_300QTL_0.1	1	$0.102^{d,A}$ (0.076)	$0.130^{b,A}$ (0.069)	$0.143^{c,A}$ (0.057)	$0.145^{cd,A}$(0.058)
	2	$0.190^{a,A}$ (0.070	$0.198^{c,A}$ (0.155)	$0.208^{c,A}$ (0.094)	$0.227^{c,A}$ (0.115)
LLD_300QTL_0.3	1	$0.135^{bcd,B}$ (0.064)	$0.192^{a,A}$ (0.039)	$0.199^{b,A}$ (0.040)	$0.200^{abc,A}$ (0.057)
	2	$0.281^{a,A}$ (0.138)	$0.309^{ab,A}$ (0.106)	$0.319^{ab,A}$ (0.085)	$0.347^{ab,A}$ (0.065)

[1] Models 1 and 2 are single- and four-trait animal models, respectively. Means followed by the different letters (lowercase letters for comparison within column and uppercase letters for comparison within row) are significantly different ($p<0.05$).

accuracies were obtained using the HLD scenario with 60 QTLs, and 30% incidence (HLD_60QTL_0.3).

Accuracies of genomic prediction for non-phenotyped cows with 25, 50, and 75% of phenotyped cows in the first and in the fourth environments are given in Table 4. In all scenarios, the accuracies of genomic prediction increased with increasing the percentage of phenotyped cows. With regard to the training sets with different percentages of phenotyped cows, no significant differences were found in the first environment. But accuracies significantly increased with the increasing number of phenotyped cows in the fourth environment. For the validation set from the fourth environment, accuracies of genomic prediction for HLD scenarios were non-significantly higher than those for scenarios with LLD. However, scenarios with 30% incidence had significantly higher accuracies compared with 10% scenarios. Increasing the QTL numbers from 60 to 300 had no significant effect on the accuracy. For the fourth environment that had phenotypic records, the lowest accuracy of 0.151 was realized for the scenario LLD_60QTL_0.1 and the largest value of 0.399 was found using the scenario HLD_60QTL_0.3 when considering 0.25% and 75% of cows with phenotypic records, respectively.

Discussion

The extent of LD, trait heritability, and incidence of the binary trait affected the accuracy of genomic prediction. The accuracies of genomic prediction were almost equal among scenarios with different numbers of QTL. González-Recio & Forni (2011) also indicated no significant difference among scenarios with different numbers of QTL (*i.e.* scenarios with 90 and 1000 QTLs had 0.33 and 0.35 accuracies of prediction, respectively). Our result also agreed with some other studies (González-Recio & Forni, 2011; Honarvar & Rostami, 2013), who applied a Bayesian approach. The higher accuracies were achieved for scenarios with HLD than scenarios with LLD, which is consistent with those results reported by Yin *et al.* (2014), Naderi *et al.* (2016), and Naderi & Sadeghi (2020). The level of LD has a substantial effect on the accuracy of genomic predictions in dairy cattle (Hayes *et al.*, 2009a). For scenarios with HLD, more SNP markers and QTLs are in linkage. Accordingly, the SNP markers can capture a larger proportion of the genetic variance of the trait (Goddard, 2009).

The heritability of the trait, as an important parameter of the genetic architecture of the trait, has a remarkable

Table 4. Accuracy of genomic predictions and standard deviations (in parenthesis) for non-phenotyped cows in the first and fourth environments with 25, 50, and 75% of phenotyped cows using a four-trait animal model over different scenarios. Scenarios consist of high or low linkage disequilibrium (HLD or LLD), different numbers of QTL (60QTL or 300QTL), and different incidences of the binary trait (10% or 30%).

Scenarios	Environment	Percentage of phenotyped cows		
		25	50	75
HLD_60QTL_0.1	First	$0.160^{a,A}$ (0.099)	$0.175^{a,A}$ (0.122)	$0.188^{a,A}$ (0.090)
	Fourth	$0.167^{b,A}$ (0.074)	$0.184^{b,A}$ (0.119)	$0.213^{b,A}$ (0.105)
HLD_60QTL_0.3	First	$0.210^{a,A}$ (0.113)	$0.226^{a,A}$ (0.132)	$0.256^{a,A}$ (0.124)
	Fourth	$0.259^{a,C}$ (0.057)	$0.342^{a,B}$ (0.071)	$0.399^{a,A}$ (0.051)
HLD_300QTL_0.1	First	$0.189^{a,A}$ (0.149)	$0.195^{a,A}$ (0.140)	$0.208^{a,A}$ (0.082)
	Fourth	$0.170^{b,A}$ (0.124)	$0.191^{b,A}$ (0.091)	$0.202^{b,A}$ (0.078)
HLD_300QTL_0.3	First	$0.213^{a,A}$ (0.133)	$0.216^{a,A}$ (0.058)	$0.238^{a,A}$ (0.098)
	Fourth	$0.264^{a,B}$ (0.085)	$0.346^{a,A}$ (0.068)	$0.351^{a,A}$ (0.050)
LLD_60QTL_0.1	First	$0.112^{a,A}$ (0.104)	$0.128^{a,A}$ (0.158)	$0.154^{a,A}$ (0.127)
	Fourth	$0.151^{b,A}$ (0.117)	$0.175^{b,A}$ (0.140)	$0.206^{b,A}$ (0.097)
LLD_60QTL_0.3	First	$0.164^{a,A}$ (0.114)	$0.167^{a,A}$ (0.119)	$0.189^{a,A}$ (0.090)
	Fourth	$0.250^{b,A}$ (0.072)	$0.281^{b,A}$ (0.097)	$0.334^{b,A}$ (0.095)
LLD_300QTL_0.1	First	$0.146^{a,A}$ (0.108)	$0.165^{a,A}$ (0.154)	$0.178^{a,A}$ (0.132)
	Fourth	$0.149^{a,B}$ (0.055)	$0.183^{a,AB}$ (0.081)	$0.195^{a,A}$ (0.067)
LLD_300QTL_0.3	First	$0.179^{a,A}$ (0.108)	$0.196^{a,A}$ (0.154)	$0.221^{a,A}$ (0.132)
	Fourth	$0.263^{a,B}$ (0.055)	$0.297^{a,AB}$ (0.081)	$0.337^{a,A}$ (0.067)

Means followed by the different letters (lowercase letters for comparison within column and uppercase letters for comparison within row) are significantly different (p<0.05).

effect on the accuracy of genomic prediction (Goddard, 2009; Hayes *et al.*, 2009a). Accuracies of genomic prediction were larger in the fourth environment than the corresponding values in other environments (Table 3). Wang *et al.* (2013), Naderi *et al.* (2016), and Naderi & Sadeghi (2020) reported high accuracies for traits with larger heritabilities. For traits with low heritability, such as fertility and health traits, accuracies of genomic prediction were lower than that for traits like milk production traits with moderate to high heritabilities (Daetwyler *et al.*, 2008; Goddard, 2009; Tiezzi *et al.*, 2018). Sun *et al.* (2014) reported accuracies of 0.16 and 0.09 for daughter pregnancy rate in Holstein and Jersey cattle breeds, respectively. In a simulation study, Hayes *et al.* (2009b) reported an increase in accuracy of genomic prediction from 0.3 to 0.7 by increasing heritability from 0.1 to 0.9. For traits with high heritability (*i.e.* phenotypic records in the fourth environment), the contribution of gene effects in phenotypic variation is high, resulting in accurate genomic breeding values (Hayes *et al.*, 2009b).

Considering the heritability of simulated traits, Bohlouli *et al.* (2017) reported quite larger accuracies compared to the results obtained from the present study. For a continuous trait with the heritability of 0.2, Bohlouli *et al.* (2017) reported accuracies between 0.46 and 0.58 using both single- and multi-trait models. But in the present study, for the same heritability, the accuracies ranged from 0.11 to 0.24 using single-trait models and ranged from 0.23 to 0.40 using multi-trait models. In a simulation study by Wang *et al.* (2017), accuracies of 0.71 and 0.40 were obtained for continuous and binary traits, respectively. Because of the binary nature (0 or 1) of traits like mastitis, calving ease, survival, and reproductive disorders, phenotypic information does not follow the same distribution as breeding values which results in smaller accuracies of genomic prediction and larger bias (Silva *et al.*, 2019). Hence, using continuous traits as suitable indirect measurements of binary traits may be promising alternatives. For instance, somatic cell count is the most appropriate indicator trait for mastitis in a view of its larger heritability than mastitis and its high genetic correlation with mastitis (Bloemhof *et al.*, 2009). The difference between the accuracies from this study and those from the previous study (Bohlouli *et al.*, 2017) was more remarkable when the incidence was 10%. In a study by Wang

et al. (2017), the accuracies of genomic prediction decreased consistently with decreased incidence from 50% to 5%. Naderi *et al.* (2016) investigated the effect of disease incidence on the accuracy of genomic prediction in cow training sets. Naderi *et al.* (2016) figured out that the prediction accuracy decreases when a lower number of sick animals are assigned to training sets. For instance, the accuracy of genomic prediction decreased from 0.47 to 0.25 with decreasing the disease incidence from 60% to 10% (Naderi *et al.*, 2016). Low accuracies for the scenarios with low incidence imply that a larger training population is needed to estimate variance components and thus to achieve sufficient accuracies of genomic prediction (Wang *et al.*, 2017).

In comparison to single-trait models, larger accuracies obtained via multi-trait animal models were consistent with the findings reported by Tsuruta *et al.* (2011), Guo *et al.* (2014), Ayalew *et al.* (2017), and Budhlakoti *et al.* (2019). This leads to the rejection of the null hypothesis and the acceptance of the alternative hypothesis that the accuracy of genomic predictions increases in the presence of G×E interactions. Guo *et al.* (2014), Jiang *et al.* (2015), and Bohlouli *et al.* (2017) demonstrated that a multi-trait model can lead to a more accurate genomic prediction by considering additional information from genetically correlated traits or from the same traits in different environments. The use of multi-trait models is more beneficial for traits with low heritability and with a small number of phenotypic records (Guo *et al.*, 2014). Hayashi & Iwata (2013) compared accuracies of single-and multi-trait models for traits with a genetic correlation of 0.7. They showed that the accuracy of GEBV from the multi-trait model was 20% larger than that from the single-trait model for a low heritability trait (h^2= 0.1). In this study, the accuracies of genomic prediction for both incidences of the binary trait (10% or 30%) via multi-trait model were almost two times larger than the corresponding accuracies obtained via the single-trait model.

Genetic correlations between traits have been used to improve the accuracy of genomic predictions in multi-trait (Jia & Jannink, 2012; Hayashi & Iwata, 2013; Bohlouli *et al.*, 2017). There were lower genetic correlations between the first and the fourth environments by low overlapping QTL groups between these two environments (Table 2). Accordingly, the accuracies of genomic prediction were lower when using animals located in the first environment as the training set and the fourth environment as the validation set and vice versa. The largest accuracy of 0.291 was achieved for cows without phenotype in the second environment when the fourth environment was used as the training set (Table S1 [suppl]). Reasons for this could be the high genetic correlation between the traits in the second and fourth environments, and the heritability of the fourth environment that was the greatest among the environments.

The number of phenotypic records to estimate GEBV affects the accuracy of genomic prediction (Calus & Veerkamp, 2007; Saatchi *et al.*, 2010; Bohlouli *et al.*, 2019). Applying four-trait models using datasets including 25% of the cows with phenotypic records in the first and fourth environments (Table 4) resulted in larger accuracies than three-trait models without any record in the first and fourth environments (Table S1 [suppl]). Since cows in the validation set were genetically related to their half-sibs in the same and other environments, these close relatives might increase the accuracy of genomic prediction (Habier *et al.*, 2010; Yin *et al.*, 2014; Bohlouli *et al.*, 2017). Accuracies of genomic prediction increased when 75% of cows had phenotypic records in the extreme environment. Because of increasing phenotypic records, the number of observations per SNP allele was increased and resulted in larger accuracies (Hayes *et al.*, 2009a).

In conclusion, more phenotypes are needed to analyze binary traits compared with continuous traits to achieve a desirable level of accuracy, especially when the incidence of binary traits deviates significantly from 50%. Finally, from a practical perspective, multi-trait models can provide more accurate genomic predictions for binary traits in the presence of G×E interactions and improve the practical breeding programs in dairy cattle. Furthermore, the genomic selection that includes G×E interaction can improve genetic gains.

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