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Short communication: Genomic prediction using imputed whole-genome sequence variants in Brown Swiss Cattle

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ABSTRACT

The accuracy of genomic prediction determines response to selection. It has been hypothesized that accuracy of genomic breeding values can be increased by a higher density of variants. We used imputed whole-genome sequence data and various single nucleotide polymorphism (SNP) selection criteria to estimate genomic breeding values in Brown Swiss cattle. The extreme scenarios were 50K SNP chip data and whole-genome sequence data with intermediate scenarios using linkage disequilibrium-pruned whole-genome sequence variants, only variants predicted to be missense, or the top 50K variants from genome-wide association studies. We estimated genomic breeding values for 3 traits (somatic cell score, nonreturn rate in heifers, and stature) and found differences in accuracy levels between traits. However, among different SNP sets, accuracy was very similar. In our analyses, sequence data led to a marginal increase in accuracy for 1 trait and was lower than 50K for the other traits. We concluded that the inclusion of imputed whole-genome sequence data does not lead to increased accuracy of genomic prediction with the methods.

Key words: genomic prediction, Brown Swiss, whole-genome sequence data

Short Communication

Genomic prediction has had a great effect worldwide, especially on dairy breeding programs. Currently, routine genomic evaluations in dairy cattle are often based on 50K SNP chip data. However, it has been shown in simulation studies that using higher-density SNP information could increase accuracy of genomic breeding values (e.g., Meuwissen and Goddard, 2010; Druet et al., 2014; Iheshiulor et al., 2016). It has been hypothesized that the use of whole-genome sequence data should in particular increase accuracy of genomic estimated breeding values (**GEBV**), as sequence data includes the causal variants. Thanks to the 1000 Bull Genomes Project an unprecedented amount of sequence data became available to all project partners (Daetwyler et al., 2014). In 2015, the fifth run of the project was released, including sequences of 1,682 bulls and cows. However, these individuals still represent only a small fraction of all individuals of the global cattle population. An alternative to sequencing more individuals is to impute sequence data into target individuals genotyped for a smaller amount of SNP. Using this approach, sequence information of a large number of individuals becomes accessible. It has been shown that imputation using the reference panel from the 1000 Bull Genomes Project is highly accurate (e.g., Daetwyler et al., 2014; Frischknecht et al., 2016); however, Druet et al. (2014) showed, in a simulation study, that especially for traits influenced mainly by QTL with low minor allele frequency (**MAF**), the increase in accuracy compared with 50K scenarios is limited. A few studies using real data to evaluate accuracy of genomic prediction have

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been published [e.g., in Holstein (van Binsbergen et al., 2015; Veerkamp et al., 2016) or Fleckvieh (Erbe et al., 2016)]; those studies found no advantage in the accuracy of genomic prediction using sequencing data over 50K SNP chip data.

The objective of the current study was to examine the effect of different SNP selection strategies on the accuracy of genomic prediction in Brown Swiss cattle. The main goal was to investigate the effect of imputed whole-genome sequence data on accuracy of genomic prediction. We estimated genomic breeding values in the Brown Swiss population using different densities of SNP data from 50K SNP data to whole-genome sequence level. Deregressed breeding values (**DRBV**; Garrick et al., 2009) were used as input phenotypes. Sequence genotypes were derived from a 2-step imputation: 50K to HD (800K) with FImpute (Sargolzaei et al., 2011), and from HD to full sequence with Beagle (Browning and Browning, 2009) and Minimac (Fuchsberger et al., 2015) using 123 Brown Swiss and Original Braunvieh animals from the 1000 Bull Genomes Project data set (Daetwyler et al., 2014) as reference individuals (Frischknecht et al., 2016). For the estimation of SNP effects, we used imputed allele dosage. For imputation, our data set, including sequenced and imputed individuals, comprised 23,001 animals with 16,184,800 SNP and small insertions or deletions. For further analyses, we excluded the small insertions or deletions and SNP with MAF <1% within the whole population and an imputation R^2 <0.1 (value provided by Minimac).

We evaluated the effect of SNP panel density on 3 traits: a reproduction trait [nonreturn rate in heifers (**NRH**); reference individuals (**ref**): n = 2,018, validation individuals (**val**): n = 240], a conformation trait [stature (**STA**); ref: n = 5,294, val: n = 596], and SCS (ref: n = 4,786, val: n = 560; Table 1). We calculated the proportion of variance that can be attributed to the SNP ($\sigma^2_{SNP} / \sigma^2_P$, where σ_{SNP} is the genetic variance attributed to SNP and σ_P is the phenotypic variance) in the data set with gcta using the reml function (Yang et al., 2010, 2011). Individuals for genomic prediction were chosen according to the reliability of the breeding value and, among these, the 10% youngest individuals were selected as validation individuals.

We estimated SNP effects for 5 different SNP selection scenarios: (1) 50K SNP chip data was used (**50K**; 38,436 SNP; average MAF: 0.247); (2) the full sequence panel was used (**SEQ**; 12,413,067 SNP; average MAF: 0.191); (3) variants with annotation missense from the Variant Effect Predictor (McLaren et al., 2016) were used (**MISS**; 33,037 SNP; average MAF: 0.182); (4) we randomly removed 1 SNP in SNP pairs from the full sequence panel that were located within a window of 10,000 SNP and showed almost perfect linkage disequilibrium (**LD**; r^2 ≥0.999999; 5,353,086 SNPs; average MAF: 0.203); (5) we performed a genome-wide association study (**GWAS**) with the full sequence panel using the bulls of the reference population and selected the 50,000 SNP with the lowest *P*-values [**TOP**; 50,000 SNP; average MAF: 0.268 (NRH), 0.241 (SCS), 0.265 (STA)]. Consequently, the number of SNP in the TOP scenario was similar to the 50K scenario. For GWAS, a mixed linear model was fitted in EMMAX (Kang et al., 2010) with allele dosage as input data using a G-Matrix from GCTA (Yang et al., 2011) and proportion of Original Braunvieh genes calculated from pedigree data as covariate. We estimated genomic breeding values using the program gbcpp (Iheshiulor et al., 2015). Using gbcpp we fitted marker effects as in BayesC (captures variants with larger effects) and a polygenic effect as a genomic BLUP term (captures genomic relationships due to polygenes; BayesC-L), which in addition to SNP makes use of the genomic relationship matrix. The model for BayesC-L can be described as

$$\mathbf{y} = 1'\mu + \mathbf{g} + \mathbf{X}\boldsymbol{\beta} + e, \qquad [1]$$

where $\mathbf{y}$ is a vector of DRBV; $\mathbf{g} \sim N\left(0, \mathbf{G}\sigma^2_g\right)$ is a vector of random polygenic effects ($\mathbf{G}$ = the genomic relationship matrix and $\sigma_\mathbf{g}$ = variance of the polygenic effect); and $\boldsymbol{\beta}$ is a vector of SNP effects with elements, which are distributed $N\left(0, \sigma^2_{SNP}\right)$ with a probability π and with probability (1 − π) equal to zero (σ_{SNP} = variance of SNP effects); $\mathbf{X}$ is a matrix of marker genotypes; and $e \sim N\left(0, \sigma^2_e / w_i\right)$ is the residual variance (σ_e = variance of residuals), with w_i being the weight of the y_i, which is in our analysis the reliability of the DRBV. For π we used a fixed value per trait, which we scaled according to the number of SNP (Supplemental Table S1; https://doi.org/10.3168/jds.2017-12890). Accuracy of genomic

Table 1. Accuracy of genomic breeding values for all scenarios[1]

Scenario[2]	SCS	STA	NRH
50K	0.556	0.538	0.397
TOP	0.502	0.478	0.324
MISS	0.504	0.495	0.347
LD	0.542	0.530	0.401
SEQ	0.548	0.527	0.403

[1]STA = stature; NRH = nonreturn rate in heifers.

[2]Scenario: 50K = SNP from 50K SNP chip; TOP = top associated variants from GWAS; MISS = variants with annotation Missense; LD = linkage disequilibrium pruned sequence data; SEQ = whole-genome sequence data.