The Process of Validating National Genomic Predictions

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Abstract

In last years many countries have implemented genomic evaluation for dairy cattle breeding. To validate national genomic models, Interbull introduced a GEBV test (Mäntysaari *et al.,* 2010) in August 2010. Almost all countries or populations have passed the GEBV test for protein yield, many of them also for milk or fat yields. However, an extension of the GEBV test to functional traits seemed to be more difficult, with unsatisfactory test results. The purpose of this study was, therefore, to describe the process of validating national genomic predictions in details using German Holstein population as an example. Several ways for improving genomic prediction were discussed with regard to genomic validation and passing the GEBV test. Increasing residual polygenic variance in SNP effect estimation was shown to be effective to make genomic prediction less biased, and it increased regression slope of the GEBV test, even for female fertility traits with low heritabilities. Using truncated national and MACE conventional evaluations for genomic validation should guarantee the validity of current national conventional evaluation model and the right time frame of phenotypic data, which is especially important for countries sharing a common genomic reference population. The current GEBV test was shown to be an important and valuable test for validating national genomic predictions.

1. Introduction

With the availability of single nucleotide polymorphism (**SNP**) chips, prediction of genetic merit for genotyped animals at an early age has become possible based on a genomic model (Meuwissen et al. 2001). In last years many countries have implemented genomic evaluation and selection in dairy cattle (VanRaden et al. 2009). In order to validate national genomic prediction models, a GEBV test (Mäntysaari et al. 2010) has been applied by countries in order to get their national genomic models approved by Interbull. The GEBV test results (Loberg et al. 2011) showed that passing the GEBV test for production traits was much easier than for functional traits. The purpose of this study was to describe the steps for validating national genomic predictions, using German Holstein as an example, and to explore the ways for making national genomic predictions less biased.

2. Current situation of the application of the GEBV test

The GEBV test (Mäntysaari *et al.,* 2010) examines how well a genomic model predicts future performance, e.g. deregressed proofs (DRP) of validation bulls. The regression slope estimate (b_1) of DRP on combined genomic breeding values (GEBV) must not significantly deviate from its expectation. In addition, squared correlation (R^2) of GEBV with DRP for the GEBV model must be greater than for a pedigree index model (Mäntysaari *et al.,* 2010). As shown in the study by Loberg et al. (2011) most countries or populations passed the GEBV test for protein yield, also for fat or milk yields. However, it seemed that estimated b_1 of functional traits such as direct longevity or female fertility deviated more often from its expectation, indicating inflated or biased national GEBV. Because biased national genomic predictions could disturb accurate international comparison, countries are requested to improve their national genomic models so that the national genomic predictions could be used for international genomic evaluation.

3. Validation of national genomic models

3.1. Steps of conducting genomic validation and the GEBV test

Three steps are needed to conduct a validation study for national genomic models and for implementing the GEBV test. The first step involves generating phenotypic data for bulls or cows, followed by a proper defining genomic reference and validation populations in second step. Finally, a special genomic test evaluation is conducted in the last step to complete the actual genomic validation.

Because genomic models, except single-step approach (Aguilar *et al.,* 2010), usually analyse only genetic effects of animals or SNP markers and no longer fixed effects or non-genetic random effects, phenotypic records need to be generated for bulls, e.g. DRP or daughter yield deviations (DYD). In order to deregress bull EBV from a national genetic evaluation, effective daughter contribution (EDC) must be calculated according to the statistical models for evaluated traits. All bulls with at least 10 EDC receive a DRP for each of 44 traits evaluated for German Holstein population. As a consequence of a shared genomic reference population with EuroGenomics countries (Lund *et al.,* 2011), DRP are needed for the non-German reference bulls. Using national EDC and heritability values of all countries and country correlations in international conventional MACE evaluation, EDC of all bulls can be calculated (Liu, 2011*a*), which are then used in subsequent deregression of MACE EBV for all Holstein bulls included in Interbull conventional evaluation. For all traits included in Interbull evaluation, MACE DRP of bulls are used in genomic evaluation or validation. However, for national traits not evaluated by Interbull, national DRP and EDC are chosen.

Table 1 shows correlation of DRP with EBV for Holstein bulls based German national and MACE evaluations from August 2009. DRP are almost perfectly correlated with EBV, with correlations above 0.99 for Holstein bulls in German national evaluation. The correlation is lower for youngest bulls due to lower reliability of their EBV. Difference (DRP – EBV) is very small, judged by genetic standard deviation of milk yield being 601 kg. All Holstein bulls included in the MACE evaluation were considered in the MACE EBV deregression as well. As foreign bulls have, on average, lower reliability of EBV on German scale, the correlation of DRP with EBV are around 0.96, lower than that of national DRP. Slightly larger differences are found between DRP and EBV from the MACE data, which can be partly explained by the difference in pedigree structure between the deregression procedure based on sire-dam pedigree and the conventional MACE evaluation based on sire-MGS pedigree.

It is important to properly define reference and validation populations for validating national genomic models, especially when EBV of current evaluation, instead of 4-years old evaluation is used (Mäntysaari *et al.,* 2010). According to the GEBV test, validation bulls are usually progeny-tested bulls having no daughters four years ago. Usually youngest, one-quarter of all genotyped proven bulls are treated as validation bulls, while the remaining three-quarter older bulls form a genomic reference population for estimating SNP effects or direct genomic values (DGV). Besides regular traits such as milk yield, early measured traits like direct genetic effects of calving traits or late measured traits like days open or direct longevity should have somewhat different validation and reference populations, because validation bulls must have conventional EBV available. Conventional daughter information of the validation bulls must be removed from the following genomic test evaluation.

Using the smaller reference population, SNP effects and DGV of validation bulls are estimated, which are combined with conventional pedigree index to obtain GEBV for validation bulls. Caution must be taken, when calculating the pedigree index and its reliability, that daughter information of the validation bulls or animals younger than the validation bulls must not be used. Regressing DRP of the validation bulls from current evaluation on their GEBV 4-years ago gives a realised accuracy of the national genomic model as well as regression coefficients

indicating (un)biased national genomic prediction (Mäntysaari *et al.*, 2010).

3.2. Experience with genomic validation

A genomic validation study (Liu *et al.*, 2011) for German Holsteins was conducted using 14,494 EuroGenomics reference and 1,377 German domestic validation Holstein bulls. It was found that the gain in accuracy due to genomics was high for traits with high heritability or reliability values, such as milk production traits and somatic cell score (SCS), because deregressed EBV of reference bulls were highly reliable. SNP effect estimates of those traits had greater variance than other traits. In the genomic validation these traits gave high accuracy (R^2) and often with greater regression slope estimate (b_1) of the GEBV test. Figure 1 shows the number of SNP markers with effect estimates equal or greater than half of marker standard deviations based on c.a. 23,000 Holstein reference bulls. It can be clearly seen that three production traits (MKG, FKG and PKG) and SCS have most big SNP markers, followed by some conformation traits , such as udder depth (UDE), stature (STA), rum angle (RAN), front teat length (FTL), and front teat placement (FTP). These traits all have high accuracy of genomic prediction (Liu *et al.*, 2011). It appears that the accuracy of genomic prediction of a trait is high, if the trait has many big SNP markers.

Genomics worked less efficiently for low heritability traits, e.g. female fertility, or traits with a small reference population, e.g. new conformation traits locomotion (LOC) or body condition score (BCS), or traits not evaluated internationally, e.g. heifer interval first to successful insemination. When low country correlations existed for a trait, e.g. overall feet and legs (OFL), foreign reference bulls contributed less and thus the accuracy of genomic prediction would be lower. Usually, those traits had fewer reference bulls and reliabilities of the reference bulls are lower. In our genomic validation study these traits were shown to have a lower R^2 value genomic prediction and more variable regression slope estimates, with a tendency of smaller b_1 value.

Even for low heritability traits, less inflated genomic prediction could be achieved by increasing residual polygenic variance in SNP effect estimation. Table 2 shows the impact of residual polygenic effect on genomic prediction based on the German Holstein validation study (Liu *et al.*, 2011). By increasing residual polygenic variance from nearly zero to 20% of total genetic variance, regression slope b_1 estimates became close to 1 as expected for five fertility traits. Those five low heritability traits would pass the GEBV test.

According to regression slope b_1 estimates from the validation study (Liu *et al.*, 2011), trait-specific residual polygenic variance was determined for German Holstein genomic evaluation. Three milk production traits and SCS had the lowest, 1%, of residual polygenic variance, whereas female fertility traits the highest, 20%. 10% residual polygenic variance was found to be best for direct longevity. Optimal residual polygenic variance for conformation traits ranged from 1% (udder depth, rump angle, front teat length), 5% (stature, rear teat placement), 10% (front teat placement), to 20% (chest width, body depth, etc.). For German Holsteins, the following traits would pass the GEBV test: three production traits, SCS, direct longevity, stature and cow non-return rate 56 days. Traits, countries or populations with a small reference population tended to pass the GEBV test more easily due to their large standard error of b_1 estimate. However, a b_1 estimate much lower than 1 still suggests that genomic prediction would be inflated.

4. Improving genomic prediction

At least six ways could be identified to improve national genomic prediction. The most effective way is to increase the size of genomic reference population, e.g. by exchanging genotypes of progeny-tested bulls with other countries. Larger genomic reference population led to higher accuracy and often higher regression slope b_1 estimate (Lund *et al.*, 2011). The second most effective way for improving genomic prediction is to increase residual polygenic variance on a trait by trait

basis, this is particularly important for low heritability traits. Thirdly, bull dams with overestimated conventional EBV should not be used as reference animals and for the calculation of pedigree index. By doing so, the bias of conventional evaluation will not be introduced to genomic evaluation. Fine tuning the deregression of national or MACE EBV is another way of improvement, e.g. using all animals in pedigree or a multi-trait model for the deregression of EBV of female fertility traits. Obviously, the single-step approach (Aguilar *et al.*, 2010) gives the most accurate genomic prediction than the current multi-step genomic models. Because foreign reference bulls in an across-country reference population do not have domestic daughters, methods need to be developed to integrate MACE evaluation of those foreign reference bulls into the single-step genomic model. Lastly, countries can fine tune their national genomic models by constantly comparing early GEBV of bulls without daughter information to later conventional EBV (Rensing and Liu, 2011).

5. Discussion and Conclusions

Interbull GEBV test requires the use of 4-years old data for validating national genomic models. However, obtaining correct data from 4-years ago is difficult when a country shares its reference population with other countries, like EuroGenomics countries, because any change in conventional evaluation by any of partner countries could make the conventional evaluation model of 4-years ago invalid. Therefore, we would like to propose that all countries conduct a special test evaluation using current conventional model with last four years data truncated and resulting national EBV be submitted to Interbull for a truncated MACE evaluation (Jorjani and Dürr, 2011). MACE proofs from the truncated Interbull evaluation would be provided to member countries for validating national genomic models. By doing so, the validity of current national genetic evaluation model and right time-frame of the validation data are guaranteed for applying the GEBV test.

Interbull GEBV test (Mäntysaari *et al.*, 2010) has been shown to be a valuable and important test for validating national genomic models. It can also be served as a useful tool for fine tuning national genomic models. A further test on regression intercept b_0 needs to be implemented. Increasing residual polygenic variance or reducing the weight on genomic relationship matrix can reduce the variance of GEBV and make genomic prediction of young candidates less inflated. This strategy works for low heritability traits, too. The GEBV test should be extended to non-production traits. In case of a shared genomic reference population between countries, only the truncated national and international evaluations can provide proper data for validating national genomic models. Passing the GEBV test should be a prerequisite for a participation in international genomic evaluation.

6. References

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Table 1. Correlation (x100) of deregressed with original EBV for Holstein bulls using German national and MACE evaluations of milk yield in August 2009.

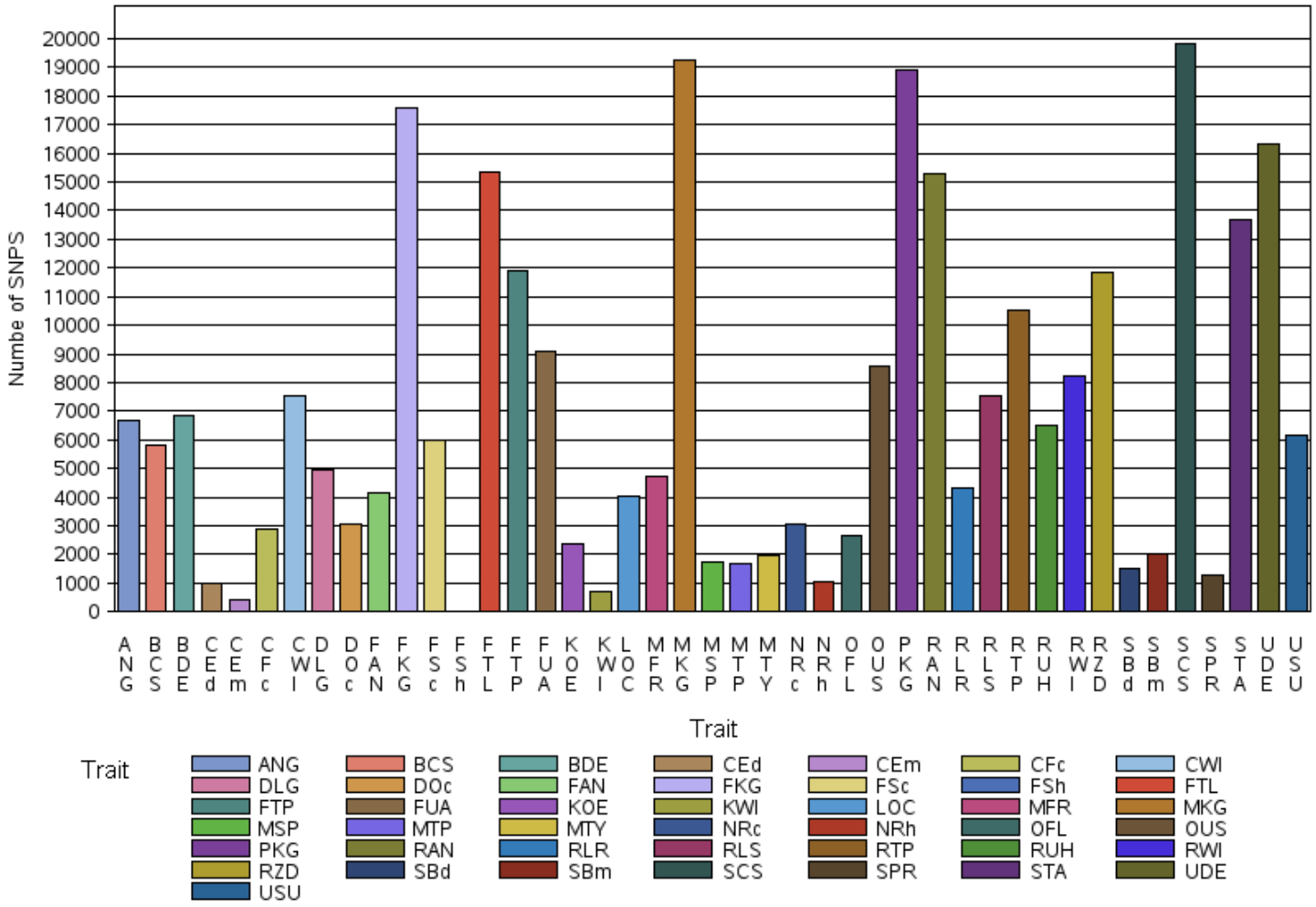
	MACE evaluation August 2009			German national evaluation August 2009		
Birth year	Nb. Bulls	Correlation	Difference†	Nb. Bulls	Correlation	Difference
1990	5685	95.8	-10.3	911	99.3	0.6
1991	5809	95.7	-9.3	924	99.3	-3.0
1992	6156	95.8	-7.1	986	99.5	-1.7
1993	5937	95.1	3.5	1063	99.4	3.2
1994	6206	96.0	6.1	1191	99.4	4.2
1995	6438	95.7	-14.5	1283	98.9	4.1
1996	6661	96.0	-16.6	1330	99.5	-1.2
1997	6816	95.5	-16.9	1381	99.3	-1.6
1998	6459	95.7	-2.7	1214	99.4	1.0
1999	6156	95.5	3.0	1192	99.5	1.2
2000	5940	95.7	-20.2	1176	99.4	1.6
2001	5963	96.0	-11.4	1140	99.5	-1.9
2002	5977	96.0	-7.3	1081	99.6	-4.0
2003	6009	95.1	-10.8	1140	99.3	-0.0
2004	4089	93.8	23.0	793	97.6	28.8
2005	387	90.2	97.0	15	90.9	7.8

† Difference is deregressed – original EBV, with unit in kg.

Table 2. Regression coefficient of deregressed EBV on GEBV of validation bulls with regard to the residual polygenic variance (female fertility traits of German Holsteins).

	Residual polygenic variance as percentage of total additive genetic variance	
Regression slope b_1 estimate	0.01%	20%
Heifer non-return rate 56 days	1.03	1.00
Cow interval calving to first insemination	0.73	0.92
Cow non-return rate 56 days	0.91	0.96
Cow interval first to successful insemination	0.55	0.99
Cow days open	0.66	1.10

Figure 1. Number of SNP markers with estimates >= 0.5 marker standard deviations



† Marker variance = total genetic variance / 45181