The fate of new mutations: genomic selection exploits new mutation variance to a much smaller degree than traditional selection
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Summary

New mutations create new genetic variance in populations and contribute to long-term response to selection. We hypothesize that genomic selection exploits new mutational variance much less than traditional selection methods, because new mutations are not in linkage disequilibrium with markers on the current SNP chips, while animals with a favourable mutation have a selective advantage with mass and pedigree-based BLUP selection. We used Monte Carlo simulation using real sequence data to generate the base generation to test this hypothesis. Genomic selection increased response to selection due to old QTL by ~33% and 1% in generation 5 and 20 compared to mass selection, respectively, while response to selection from new mutations was 65-85% and 61% lower than with mass selection in generation 5 and 20, respectively. In genomic selection, genetic variance due to old QTL was much faster eroded, while new mutational variance did not increase much, resulting in a ~65% and ~43% lower total genetic variance in generation 20 with genomic selection, compared to mass and pedigree-based BLUP selection. In summary, we showed that genomic selection hardly exploits new mutational variance and erodes genetic variance much faster than mass and BLUP selection. Future research should focus on developing sustainable genomic selection strategies to optimize long-term response to selection, exploiting new mutational variance.

Keywords: de novo mutation, genomic selection, long-term selection response, selection

Introduction

Mutations in gametes are frequently occurring and generate new genetic variance when they are in genes affecting the traits of interest. The contribution of new mutational variance to selection response is small in the short term but becomes substantial after 10-20 generations, because mutations cumulate and some may increase in frequency, either due to drift or due to selective advantage. Hill (1982) derived expressions for long-term selection response based on new mutations. Based on meta-analysis on several studies and theoretical analysis, Houle et al. (1996) showed that the standing genetic variance is replaced by new mutations in 50-120 generations based on the assumption of mutation-selection balance and depending on the type of trait. This shows that new mutational variance is not unimportant for medium and long-term selection response.

Selection strategies may differ in their ability to exploit new mutational variance. With
traditional selection strategies, animals are selected based on phenotypic information, e.g. own performance with mass selection or pedigree-based BLUP-EBV combining information of own performance and phenotypes of relatives. With these selection strategies, animals with favourable mutations have a selective advantage. With genomic selection, however, animals are selected before phenotypes are collected and selection candidates that carry favourable mutations would not have a selective advantage. Furthermore, the effect of mutations in relatives that may appear in the reference population are likely not to be captured with markers, because mutations are not in linkage disequilibrium (LD) with SNP-markers. As a consequence, favourable mutations will be easily lost with genomic selection due to drift, while unfavourable mutations may persist if they do not get lost by drift. Some research has been done on optimizing long-term response to genomic selection (Goddard, 2009; Jannink, 2012) or on the effect of mutations on the accuracy of genomic prediction (Casellas and Varona, 2011; Casellas et al., 2013). However, no research has been done on the contribution of new mutation variance to response to selection, comparing genomic and traditional selection schemes.

The aim of this study was to test the hypothesis that genomic selection exploits new mutational variance less than traditional selection. We used Monte Carlo simulation and real sequence data of Holstein cattle as a base. We compared selection response and genetic variance for genomic, mass, and pedigree-based BLUP selection for 20 generations using truncation selection.

Material and methods

Simulation based on whole-genome sequence data
We simulated a typical livestock breeding program in which 50 sires and 200 dams were selected to produce the next generation. Each dam produced 10 offspring, 5 males and 5 females. We used whole-genome sequence data of 369 Holsteins from the 5th run of the 1000 bull genome project to generate the base generation of 50 males and 200 females, excluding the 81 sequenced sires that had sequenced sons to reduce the relationships among base animals. The first three chromosomes were used, from which 1 in 20 Single Nucleotide Variants (SNV) were selected (~300,000) to limit computing time and storage capacity. We randomly sampled 5000 QTL positions among the polymorphic SNPs and selected 20,000 SNV as SNP markers among the rest of the sites with a minor allele frequency above 0.05. The QTL-effects were drawn from a gamma distribution with shape parameter 0.4; heritability was 0.3. The number of recombinations and mutations per gamete were drawn from Poisson distributions and locations of recombinations and mutations were randomly assigned across the genome. Mutations were always in monomorphic SNV. The mutation rate per individual offspring was 0.5 and mutation effects were drawn from a gamma distribution with shape parameter 0.4, the same as for existing QTL. The sampled mutation effects were scaled, such that the mutational variance was 0.001Ve (environmental variance) (Hill, 1982; Houle et al., 1996). Phenotypes were the sum of the QTL-effects, mutation effects and random environmental effects. Environmental effects were sampled from a normal distribution with Ve such that heritability was 0.3 in the first generation.

Selection strategies
Truncation selection was done on phenotypes (mass selection), pedigree-based EBV (BLUP selection) or genomic EBV (GEBV, genomic selection). Parents were randomly mated with no control on inbreeding. EBV were estimated with ASREML4.1 (Gilmour et al. 2014) and
GEBV were estimated with MTG2 (Lee and Van der Werf, 2016). For GBLUP, the genomic relationship matrix (GRM) was constructed either using the VanRaden (2008) method, which favours common variants, or using the Yang et al. (2010) method, which favours rare variants. Genomic relationship matrices were made with calc_grm software (Calus and Vanderplas, 2016). To limit computing time, GEBV were estimated on at most the last 5 generations of animals before the generation of selection candidates, resulting in a maximum of 10,000 animals for the reference population. To make the difference between mass/BLUP selection and genomic selection as large as possible, it was assumed that selection candidates had phenotypes at the moment of selection (e.g. growth) with mass and BLUP selection, whereas selection candidates had no phenotypes with genomic selection, i.e. selection just after birth. For each scenario, 100 replicates were run for 20 generations.

Results & Discussion
For all selection strategies, response due to old QTL decreased, while response due to new mutations increased over time. (Figure 1, Table 1). Genomic selection outperformed mass and BLUP selection for response to old QTL, while response due to new mutations was much smaller than with mass or BLUP selection. There was hardly any difference between the two genomic selection strategies (estimating GRM with VanRaden vs. Yang et al.). When comparing total response to selection in generation 20, mass selection had a higher response than genomic selection (which had higher response than BLUP selection), because of the larger response due to new mutational variance. Here we assumed that generation intervals did not differ between selection methods, while in practice the genomic selection scheme is likely to have smaller generation intervals and therefore it is expected that response per year is higher with genomic selection than with mass and BLUP selection. Genetic variance due to old QTL decreased for all scenarios, but the decrease was the greatest for genomic selection and least for mass selection. Furthermore, mutational genetic variance was larger with mass and BLUP selection than with genomic selection. As a consequence, the total genetic variance with mass and BLUP selection was 185 to 191% and 72 to 75% larger than with genomic selection in generation 20. In summary, genomic selection exploited new mutational variance to a much lesser degree and eroded the total genetic variance much faster than mass and BLUP selection.
Proceedings of the World Congress on Genetics Applied to Livestock Production, 11.415

*Figure 1. Response to selection per generation for old QTL (A) and new mutations (B).*

*Table 1. Genetic gain based on old QTL, based on new mutations, and total genetic gain, and the old and new genetic variance in generation 5 and 20 for mass, BLUP and genomic selection (GS) using either VanRaden or Yang to construct the genomic relationship matrix.*

<table>
<thead>
<tr>
<th>Gen</th>
<th>Selection strategy</th>
<th>Gain old</th>
<th>Gain new</th>
<th>Gain total</th>
<th>Gain new /gain total</th>
<th>Old genetic variance</th>
<th>New genetic variance</th>
</tr>
</thead>
<tbody>
<tr>
<td>5</td>
<td>mass</td>
<td>0.442</td>
<td>0.005</td>
<td>0.447</td>
<td>0.011</td>
<td>0.252</td>
<td>0.004</td>
</tr>
<tr>
<td></td>
<td>BLUP</td>
<td>0.491</td>
<td>0.005</td>
<td>0.496</td>
<td>0.010</td>
<td>0.226</td>
<td>0.004</td>
</tr>
<tr>
<td></td>
<td>GS VanRaden</td>
<td>0.581</td>
<td>0.002</td>
<td>0.582</td>
<td>0.003</td>
<td>0.195</td>
<td>0.004</td>
</tr>
<tr>
<td></td>
<td>GS Yang</td>
<td>0.590</td>
<td>0.001</td>
<td>0.591</td>
<td>0.001</td>
<td>0.198</td>
<td>0.003</td>
</tr>
<tr>
<td>20</td>
<td>mass</td>
<td>0.273</td>
<td>0.068</td>
<td>0.341</td>
<td>0.200</td>
<td>0.155</td>
<td>0.041</td>
</tr>
<tr>
<td></td>
<td>BLUP</td>
<td>0.230</td>
<td>0.062</td>
<td>0.292</td>
<td>0.213</td>
<td>0.090</td>
<td>0.028</td>
</tr>
<tr>
<td></td>
<td>GS VanRaden</td>
<td>0.276</td>
<td>0.027</td>
<td>0.302</td>
<td>0.088</td>
<td>0.050</td>
<td>0.017</td>
</tr>
<tr>
<td></td>
<td>GS Yang</td>
<td>0.275</td>
<td>0.027</td>
<td>0.302</td>
<td>0.089</td>
<td>0.052</td>
<td>0.017</td>
</tr>
</tbody>
</table>

These results show that optimization of long-term response to genomic selection is needed, as well as maintenance of genetic variance. Goddard (2009) and Jannink (2010) proposed methods to optimize long-term response to genomic selection by putting more weight on rare favourable alleles and less weight on common favourable alleles. For new mutations, such a strategy is probably not enough, because new mutations are not in LD with markers on the chip. Furthermore, it is clear that the contribution of new mutational variance to long-term response to selection is only substantial if new mutations receive some selection pressure to increase the frequency of favourable mutations. The use of mutational relationship matrices or relationship matrices based on haplotype information is expected to better exploit new mutational variance.

**Conclusions**

We showed that genomic selection (GBLUP) hardly exploits new mutational variance and erodes genetic variance much faster than mass and pedigree-based BLUP selection. As a consequence, genomic selection is superior for short-term response to selection, but not for long-term response to selection. Future research should focus at developing sustainable genomic selection strategies to optimize long-term response to selection.

**List of References**


