

Including Gene Edited Sires in Genetic Evaluations

Leticia P. Sanglard
Garret M. See
Matthew L. Spangler

Summary with Implications

A simulation study investigated and provided potential solutions to practical issues that could arise from including gene-edited sires in routine genetic evaluations. Gene-editing is a technique for adding, deleting, or replacing nucleotides in the genome. Editing nucleotides controlling important socioeconomic traits (e.g., growth, carcass, disease susceptibility) is expected to improve rates of genetic gain. However, targeted alterations of the genome can affect the relationship among individuals and, consequently, introduce bias in Expected Progeny Differences. The current study illustrated that, indeed, Expected Progeny Differences for the progeny of edited sires were underestimated. Consequently, these animals would be less likely to be selected as parents for subsequent generations. Therefore, if edited sires are introduced into genetic evaluations, the statistical models used in the evaluation need to appropriately accommodate the changes among animals that the targeted gene edits create, and adjusting the kinship among animals is one way to do this. Without accounting for these targeted changes Expected Progeny Differences will be biased, and selection decisions could be made incorrectly.

Introduction

Gene-editing is an emerging technology for adding, deleting, or replacing nucleotides in the genome that offers the potential to increase the frequency of favorable alleles. Although current governmental regulation in the U.S. creates undue burdens for bringing the full potential of this technology to fruition, it is important for genetic evaluation service providers to consider

Table 1: Average absolute bias and dispersion of EBV in generation 8 averaged over all relationship matrices, number of gene-edited QTN, and number of gene-edited sires.

| Status | Strategy ¹ | Average absolute bias | Slope ² |
|----------------------------|-----------------------|-----------------------|--------------------|
| Progeny of non-gene-edited | Non-weighted | 0.79 (0.01) | 0.90 (0.06) |
| Progeny of non-gene-edited | Weighted | 0.78 (0.01) | 0.95 (0.01) |
| Progeny of gene-edited | Non-weighted | 1.36 (0.50) | 0.84 (0.11) |
| Progeny of gene-edited | Weighted | 0.90 (0.14) | 0.93 (0.04) |

¹If the relationship matrix was weighted based on the QTN effect (Weighted) or not (Non-weighted);

²Slope of the regression of true BV on EBV, representing the dispersion of EBV. The expected value is 1.

the potential impact of gene-edited animals and their offspring in routine genetic evaluations. This is particularly true when the edits are related to quantitative traits for which Expected Progeny Differences (EPD) exist or traits that are genetically correlated to traits with EPD. It is possible that gene-editing technology could enable large numbers of edits controlling important socioeconomic traits to be performed and, when coupled with genomic selection, could prove a powerful means of improving genetic gain for complex traits. However, genetic evaluations are based on the relationship among individuals, whether through pedigree (numerator relationship, A matrix), marker-based (genomic relationship, G matrix), or a combination of pedigree and genomic relationships (H matrix). Changing nucleotides in the genome can affect these relationships and, consequently, introduce bias in EPD. The objective of this study was to quantify differences in Estimated Breeding Values (EBV; twice an EPD) using an 8-generation simulated beef cattle population that included gene-edited sires and their progeny.

Procedure

The simulated genome contained 99 quantitative trait nucleotides (QTN) and 6,000 single nucleotide polymorphisms (SNP) distributed across 3 chromosomes. A moderately heritable trait ($h^2=0.4$) was simulated. In total, the population consisted of 8 generations and a total of 13,100 animals.

After 7 generations, gene-edited sires ($n=1, 25,$ or 50) were introduced. The number of QTN edited (% additive variation controlled by the QTN) was 1 (2%), 3 (5%), or 13 (20%). All scenarios were replicated 15 times. Genetic evaluations were performed using pedigree (A), genomic (G), or combined (H) kinship matrices. Relationships were also weighted (w) based on the proportion of genetic variance explained by the edited QTN. Scenarios were compared based on the accuracy of EBV (correlation of true BV (TBV) and EBV), which reflects the potential re-ranking of individuals, average absolute bias, which reflects the error around the estimation of EBV, and the slope (b_1) of the regression of TBV on EBV, which reflects the dispersion of EBV.

Results

The average absolute bias and EBV dispersion in generation 8 averaged over all relationship matrices, number of edited QTN, and number of gene-edited sires are reported in Table 1.

Overall, the average absolute bias and the degree to which EBV were under-dispersed increased as the number of gene-edited sires and edited QTN increased ($P \leq 0.001$). Correspondingly, differences in the average absolute bias and EBV dispersion between the progeny of gene-edited vs. non-gene-edited sires and between weighted vs. non-weighted relationship matrices were greater when more sires or QTN were edited. Estimated Breeding Values of prog-

eny of gene-edited sires were associated ($P \leq 0.001$) with more error (greater average absolute bias) when the evaluation used non-weighted relationship matrices and more than one sire or more than one QTN were edited. Differences in EBV dispersion between weighted vs. non-weighted relationship matrices were significant ($P \leq 0.001$) when 25 or 50 sires were edited, with EBV dispersion from weighted relationship matrices closer to the expected value of 1. In generation 8 (included offspring from gene-edited sires), weighting the relationship matrices increased the accuracy by 3%

($P = 0.003$). Given the EBV of the progeny of gene-edited sires were underestimated, re-ranking of individuals in generation 8 was expected, disfavoring the selection of the progeny of gene-edited sires.

Conclusion

In general, the EBV of the progeny of gene-edited sires were associated with greater error (average absolute bias) and were under-dispersed to a greater degree than the EBV of the progeny of non-gene-edited sires. Weighting the relationship

matrices increased the accuracy of EBV when the gene-edited sires were introduced, decreased the average absolute bias, and led to EBV dispersion closer to the expected value of 1. Therefore, when gene-edited parents are included in the genetic evaluations, methods such as weighting the relationship matrices should be considered to avoid biased EPD that could lead to incorrect selection decisions.

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Leticia P. Sanglard, postdoctoral student
Garret M. See, postdoctoral student
Matthew L. Spangler, professor, University of Nebraska-Lincoln