Use of Mate Selection Software to Manage Lethal Recessive Conditions in Livestock Populations

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ABSTRACT: Lethal loci with low and intermediate recessive allele frequencies were simulated into a real beef cattle population. The impact of selecting against the number of lethal alleles and recessive lethal genotypes in progeny of available selection candidates were examined in terms of compromised genetic gain relative to selection in the absence of lethal loci considerations. Six lethal loci could be managed with relatively little impact on genetic gain, especially at low allele frequencies; however with 100 lethal loci, decreasing both carrier and homozygous lethal progeny resulted in considerable compromise in genetic gain. Mate selection against homozygous progeny resulted in a superior outcome in terms of genetic gain and reduction in progeny lost as compared to selecting against carrier progeny. As the number of known lethal loci increases, selection strategies will need to optimize balance between compromises in genetic gain and reduced embryo mortality.
Keywords: recessive, mate selection, lethal

Introduction

Management of deleterious recessive conditions in breeding populations is likely to become increasingly complex with the use of genomic information. It has been estimated that the average human carries approximately 10^3 damaging non-synonymous SNPs that collectively cause a reduction in fitness (Sunyaev et al. (2001)). Studies are underway to discover low-frequency recessive lethals by looking for loci with 'missing homozygotes' in livestock populations (VanRaden et al. (2011)). Efforts are in progress to obtain the full genome sequence of key sires from a variety of breeds to identify SNPs that are predicted to have a disruptive effect on protein structure and impair fertility (Georges (2012)).

Historically, such conditions were managed by test matings between suspected carriers and heterozygotes, or more recently by identification of carriers using genetic testing. Some breed associations have chosen to not register these carrier individuals, and some breeders have chosen to avoid using these animals irrespective of their genetic merit or the frequency of the undesirable allele in the population. This approach is not optimal from the perspective of genetic improvement since, in some cases, the overall breeding value of carrier animals outweighs the economic penalty of their carrier status (Charlier et al. (2008)).

The objective of this study was to simulate 6 or 100 lethal SNP loci of differing allele frequencies (low and intermediate) and explore the impact of different mate selection strategies to manage these hypothetical lethal recessive conditions in a herd of pedigreed beef cattle.

Materials and Methods

Data. PopSNP (Kinghorn, unpublished), a program that populates SNP data into an existing pedigreed dataset, was used to simulate either intermediate frequency (Mean 0.195; range 0.005- 0.46), or low frequency (Mean 0.0401; range 0.005-0.08) SNPs into a data set from an Angus beef herd pedigree consisting of 169 female selection candidates, 85 male selection candidates and 546 ancestor records. As a point of reference, the minor allele frequency of recessive lethal conditions in the Australian Angus population at the time of their discovery was approximately 0.04, or approximately 8% carriers (Teseling and Parnell (2013)). These records included a selection index value ($Beef) for each individual. A genome size of 30M consisting of 29 chromosomes based on the size of the bovine chromosomes was modeled, and recombination fractions were calculated assuming a Kosambi mapping function. Ancestors and selection candidates with lethal "aa" genotypes were assumed dead and not allowed in the pedigree.

Mate Selection MateSel is a software program for tactical implementation of breeding programs, based on an evolutionary algorithm (Kinghorn 2011). It accommodates the prevailing technical and logistical issues, including genetic gain, genetic diversity, trait distributions and the management of allele and genotype frequencies for individual genetic markers.

To collectively manage many recessive lethal loci, MateSel was modified to include two additional parameters; 1) LethalA and 2) LethalG. LethalA is the predicted number of recessive lethal alleles, across nominated loci, in the progeny of each mating. Given that the parents have zero probability of being homozygous lethal at any locus, the maximum value for LethalA is 0.5 + 0.5 = 1 per locus where both parents are heterozygotes. So LethalA ranges from 0 to the number of loci under consideration. This variable can be used to select against the number of recessive lethal alleles in the population, using various weightings. LethalG is the predicted number of recessive lethal genotypes (i.e. aa) in the progeny of each mating, across all loci. This is not fully related to the probability of dying because an embryo cannot die twice if it is homozygous recessive for two or more lethal loci. But for the very low incidence of homozygotes at more than one loci, the difference is trivial, and equivalence is assumed here for simplicity. Given that the parents have zero probability of being homozygous lethal at any locus, the maximum value for LethalG is 0.5 * 0.5 = 0.25 per locus where both parents are heterozygotes at all loci. LethalG can therefore range from 0 to 0.25 times the number of loci considered. LethalG is used to select against the incidence of lethally affected progeny from the current matings.

Mate selections for all 169 candidate females were initially allocated based on a target relationship of 25 degrees (see Kinghorn, 2011, for explanation) between genetic gain (Progeny Index, xG) and parental coancestry (xAx/2) without consideration of recessive alleles. No one sire was allowed to be used more than 50 times. Analyses were then performed applying increasing levels of emphasis (weightings of 0.1, 1, 5, 10 and 100) on reducing mean LethalA (predicted number of recessive lethal alleles in the progeny), or LethalG (predicted number of lethally affected progeny). Four scenarios were examined including managing 6 or 100 loci selected from either the high or low frequency SNP distributions. The effect of these various mating strategies was examined in terms of average progeny index value from the resulting matings, and the predicted reduction in LethalA and LethalG in the progeny.

Results and Discussion

MateSel was initially used to optimize mate allocations in the absence of any allele information and it produced a solution that resulted in a progeny index average of ~71.5 (top of green line in Figure 1). All subsequent analyses were compared to this "zero" selection against recessive alleles.

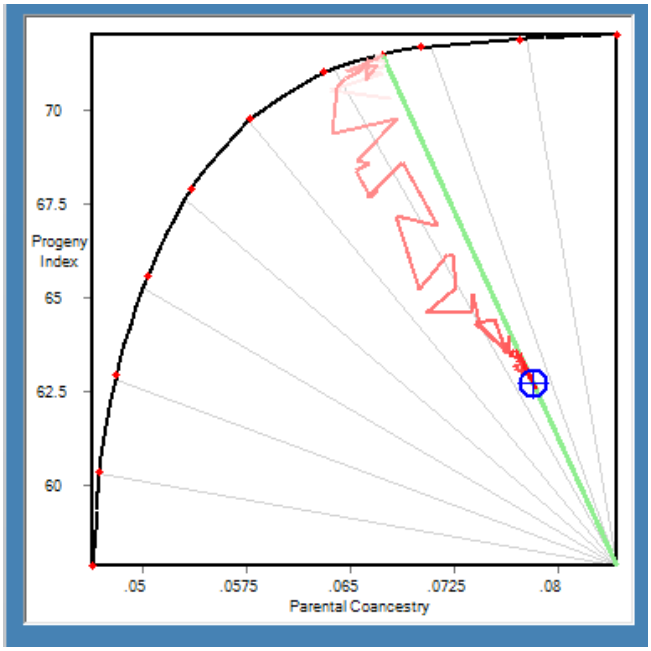

Figure 1. A MateSel run showing considerable decrease in Progeny Index value achievable, with associated increase in parental coancestry (blue circle) when strongly directed to avoid matings that result in recessive lethal genotypes.

Selection against low frequency alleles at 6 loci had little impact on genetic progress, as there were very few matings that might have resulted in either a carrier or lethally affected progeny (Figure 2A). Strong selection against a small number of intermediate frequency alleles decreased genetic gain to 92% when selecting against alleles (LethalA), and to 94% when selecting against affected genotypes (LethalG).

Strong selection against carriers when there were 100 loci modeled decreased genetic gain to 86% when alleles were at low frequency, and 81% when they were present at intermediate frequency (Figure 2A). Using a selection strategy that focused only on avoiding embryo mortality improved this outcome and improved progeny index values to ~ 90% of that possible. At all weightings, selection on LethalG achieved a superior outcome in terms of decreased impact on rate of genetic gain and reduction in progeny lost as compared to selecting on LethalA.

Losses due to embryo mortality were negligible in the case of 6 lethal loci and low allele frequencies, and a minor relative weighting (1) was sufficient to reduce this value to zero when alleles were present at an intermediate frequency (Figure 2B). In the case of a high number of loci, it was not possible to bring the incidence of embryo mortality to zero irrespective of weighting used. Some carrier progeny were obtained in all scenarios (Figure 2C).

The compromise in genetic gain that is required to reduce embryo mortality depends upon the number of lethal loci, and allele frequencies (Figure 2D). In the case where there are a large number of lethal loci, considerable compromise in genetic gain was required to reduce the incidence of embryo mortality. Ideally, the economic weighting associated with embryonic loss should be incorporated into the selection index to ensure the optimal balance between compromise in genetic gain and reduced embryo mortality.

Conclusion

Management of deleterious recessive conditions can be achieved by mate selection software that decreases the incidence of lethal homozygous progeny. The compromise required in terms of genetic gain is dependent upon allele frequencies, number of lethal loci and relative weighting that is placed on avoiding embryonic mortalities.

Acknowledgements

The authors acknowledge Mike Kasten and Sally Northcutt, American Angus Association for herd and pedigree data; and funding support form National Research Initiative Competitive Grant no. 2013-68004-20364 from the USDA National Institute of Food and Agriculture.

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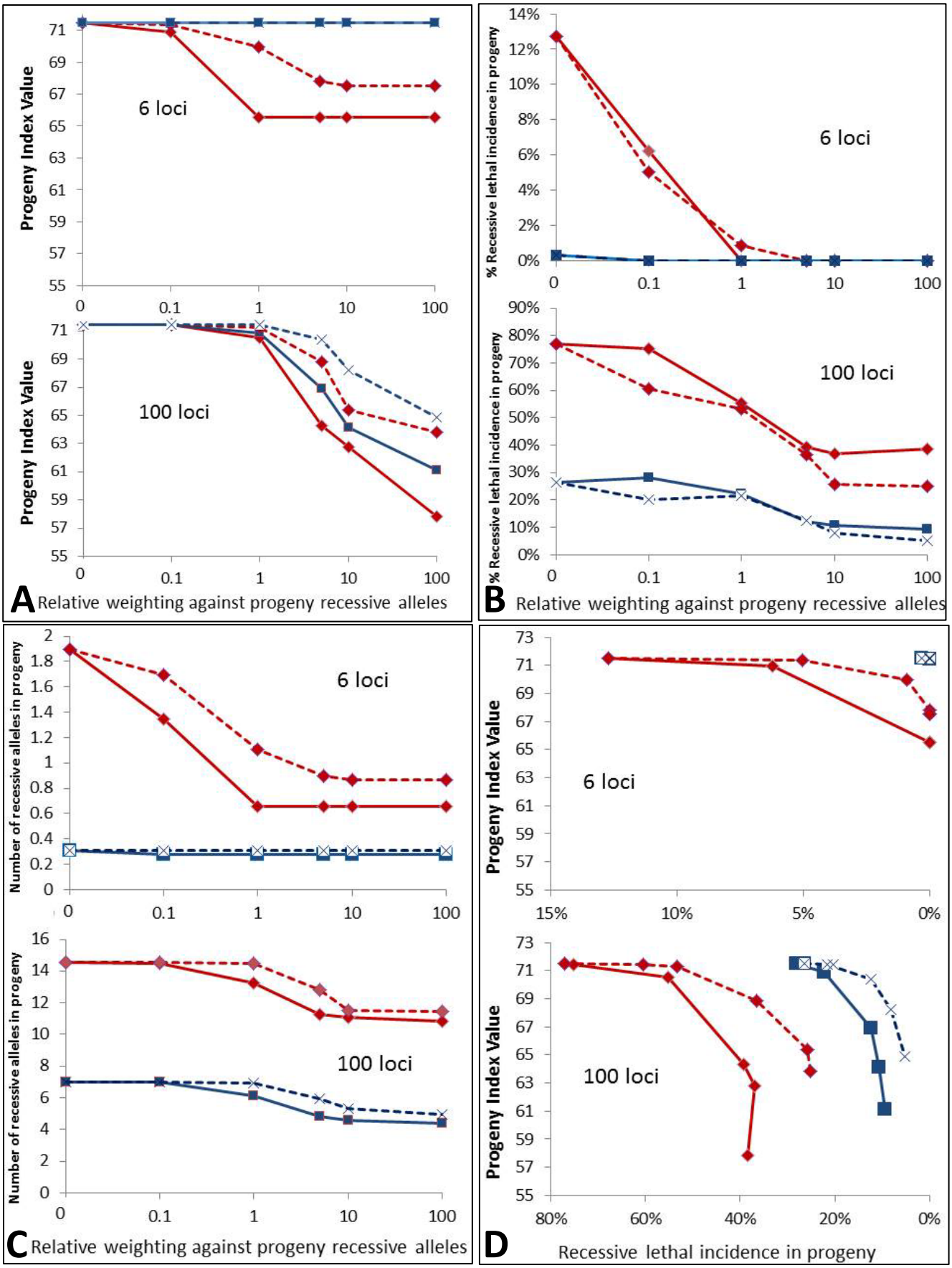

Figure 2. Effect of varying levels of selection against number of recessive alleles (LethalA, Solid line) or homozygotes (LethalG; Dashed Line) for intermediate (mean 0.195; red ♦) or low (mean 0.04; blue ■, X) SNP allele frequencies on A) Progeny Index Value; B) % recessive lethal incidence in progeny; C) number of recessive alleles in progeny; and D) relationship between Progeny Index value and % recessive lethal incidence in progeny for 6 or 100 lethal loci.