Proposed Strategy for Selection Against Recessive Genetic Defects Through a Combination of Inbreeding and DNA Markers

R. Mark Thallman, John W. Keele, and Gary L. Bennett

U.S. Meat Animal Research Center
Clay Center, NE USA

Overview

- Introduction
- Mating Plan
- Mapping Efficiency for Completely Recessive Defects
- Sub-Clinical Defects
- Embryonic Mortality
- Value of Inbred Progeny
- Conclusions

Introduction

- Recessive defects have gained a lot of attention in the past few years.
- DNA tests have been effective in reducing their frequency to inconsequential levels.
- The only way to prevent new recessive defects from becoming problems is to discover them before they reach high frequencies.
- The most practical way to discover recessive defects seems to be through inbreeding.
  - Most breeding programs are designed to cover them up.

Managing Genetic Defects

- Is it genetic?
  - Often this is not clear
- What is the mode of inheritance?
  - Recessive, Dominant, Epistatic
  - Inbreeding is the most effective way to determine whether recessive defect or not
- Where in the genome is the defect?
- Develop markers to track the defect through multiple generations

History of Inbreeding

- Inbreeding has been tremendously powerful in plant breeding.
- The early pioneers in Animal Breeding recognized theoretical advantages of and conducted a number of experiments on inbreeding.
- However, the general conclusion was that the challenges were too great to make inbreeding practical in livestock and it is used much less today than 50 years ago.
- The feasibility of inbreeding should be reevaluated in light of recent advances in DNA marker technology.

Objectives

- Propose a strategy that could make it practical to systematically identify, map, and select against recessive alleles.
- Consider some of the challenges in implementing this strategy and how they might be overcome.
- Explore some potential secondary benefits of this strategy.
- Discuss some general principles of managing genetic defects in breeding programs.

Current Approach to Reducing Genetic Defects

- Can be characterized as "putting out fires".
- Applies only to those recognized as being important problems within breeds.
- Attempt to find causative mutations or other polymorphisms in very tight linkage disequilibrium with causative polymorphism.
- Use DNA testing of important sires to select against the defects.

Proposed Strategy

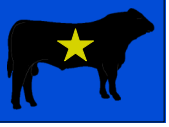
- Breed young sires identified for progeny testing to enough females to produce 25-50 progeny.
- Breed elite sires that pass progeny test to daughters to produce 16-32 inbred progeny expected to result in 2 to 4 affected progeny for any recessive defect carried by the sire.
- Map any defects observed using both affected and unaffected progeny.
- Select against genomic regions likely to contain defects in descendants of the tested sires.

Designation of Tested Sires

- Need a way to differentiate sires that have been through the process so that breeders have an incentive to go through it.
- I am going to use a "Gold Star" to designate bulls that have gone through the process, but probably need some logo to designate these bulls in promotional materials.

The Gold Star Designation

- Should indicate that the bull is enrolled in the program.
  - Should be applied at the time of enrollment.
- It is not an indication that the bull is free of defects.
  - Instead, it is an indication that defects that the bull carries may be selected against and managed through DNA testing.



Proposed Strategy

- What I am outlining here is only one of many specific ways of approaching the problem.
- Many variations on it are possible and would fit various circumstances better than what I propose here.
- The focus of this presentation is on the concepts rather than on the specifics.

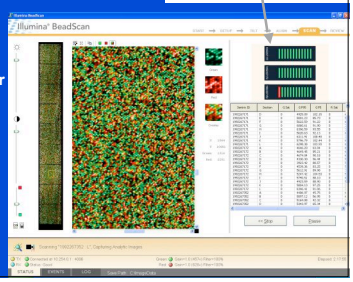
50,000 Markers on a Chip

Illumina Infinium Bovine BeadChip

~ 50,000 SNP markers across the bovine genome

-High resolution (1 SNP per 60,000 base pairs)

- Multiple breeds used for SNP discovery



BARC (ARS)
USMARC
University of Missouri
University of Alberta

Managing Defects Would Require a New Category of DNA Testing Services

- 50K chip could form the backbone
- Lower density SNP sets would be useful
- Some level of customization probably necessary

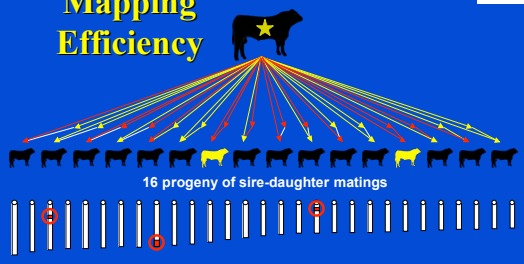
Managing Defects Would Require a New Category of DNA Testing Services

- Breeders would need assurance that the appropriate DNA testing services would be available before initiating sire-daughter matings.
- But, DNA testing companies would need assurance that there would be a market before investment in developing the appropriate services.

Mapping Efficiency

- 2 to 4 affected progeny from a set of 16 sire-daughter matings provide sufficient information to map a recessive defect reasonably well, provided:
  - The unaffected sibs are available for DNA analysis.
  - The phenotypes are unambiguous.

Mapping Efficiency



- On average, 2 affecteds and 14 nonaffecteds are sufficient to map a defect to 3.2 chromosomal regions with a total length of 33.5 cM.

Mapping Efficiency

- On average, 3 affecteds and 13 nonaffecteds are sufficient to map the defect to 1.6 chromosomal regions with a total length of 17.6 cM.

Mapping Efficiency

- With four or more affected progeny, the defect is usually mapped to a single region with a length of less than 10 cM.

Selection Strategy

- DNA testing makes it unnecessary to cull tested sires which have defects.
- The selection occurs in the tested sires' descendants and it occurs before any investment in progeny testing them.
- Selection may also occur in collateral relatives of sires in which defects were identified and mapped.
- The approach does not need to affect generation interval substantially.

What Type of Defects?

- Severe abnormalities/lethals
- Sub-clinical recessive effects that reduce production and/or cause non-conformities, but that would not currently be generally recognized as genetic defects.

Recognition of Genetic Defects

- Likely most effective through visual inspection.
  - Look for small sets of progeny that share anomalies, structural unsoundnesses, or causes of unthriftiness that appear to have a common physiological basis.
- Much easier if all of the progeny inbred to a particular sire are contemporaries in time, location, and management.

Hypothetical Illustration of Sub-clinical Defect

Hypothetical Illustration of Sub-clinical Defect

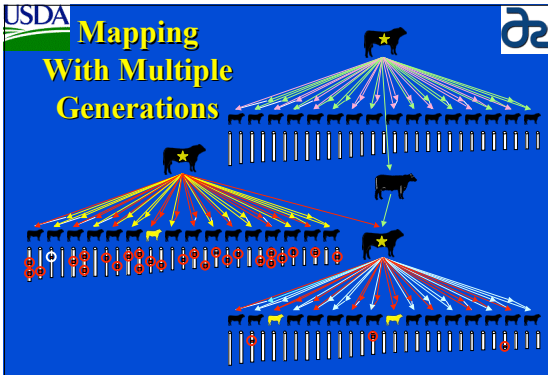
Recognition of Genetic Defects

- In many cases, it will not be possible to determine unambiguously whether a particular anomaly is a recessive defect or not.
- However, if the same anomaly appears again in a closely related sire, combining the two families may make it clear whether or not the anomaly is recessive.
  - Combining families may also provide sufficient information to map the defect unambiguously.

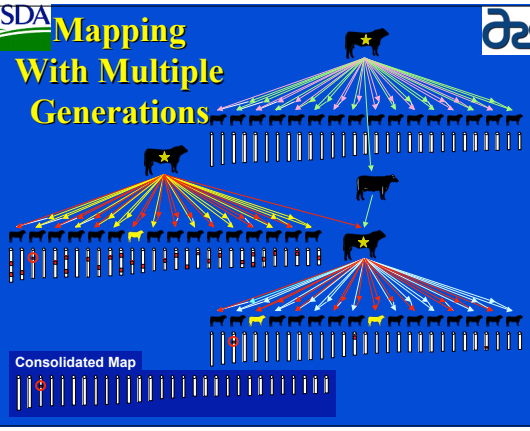
Mapping Efficiency of Defects that are Not Clearly Distinguishable

- Would be considerably less than for effects that are unambiguous.
- Would require more affected progeny, preferably through more families, to achieve the same level of confidence.

Mapping With Multiple Generations



Mapping With Multiple Generations



Identifying and Mapping Embryonic Lethals

- Could be one of the greatest opportunities for improving reproductive performance.
  - It is not known to what extent recessive embryonic lethals contribute to loss of fertility.
  - However, it seems plausible that they are an important cause. If they are, there probably are a large number of them, each at low frequency.

Identifying and Mapping Embryonic Lethals

- Mapping these defects would be quite challenging because it is generally not practical to obtain DNA on the affected embryos.
  - However, combining inbred progeny from multiple, closely related sires might make it possible.
- There is also potential for improving the efficiency of identifying lethals if ET was used to produce the inbred progeny.
  - This could be particularly effective for identifying lethals that have visible effects by Day 7 of development.

Quantitative Genetics Approaches to Managing Sub-clinical Defects

- Perhaps, we could include sire-specific inbreeding depression in NCE.
  - This would essentially be an additional EPD for inbreeding depression.
  - It would tell us how likely a particular sire is to carry a sub-clinical defect and whether it would be worthwhile to try to map it genetically.
  - This would be based on comparison of inbred vs. non-inbred progeny within contemporary groups.
  - It would require that planned inbreeding be used fairly routinely within the breed being evaluated.
  - Selection based on it would be practical only because of the availability of DNA marker technology.

Quantitative Genetics Approaches to Managing Sub-clinical Defects

- Sire-specific inbreeding depression is based on the concept that being right more often than you are wrong in the face of uncertainty generates more progress than only selecting when you are certain you are right.
  - This is essentially the concept of whole genome selection.
  - It is also the basis for the last fifty years of progress in traditional cattle breeding.
- It *may* be our best chance at reducing variation in commercial cattle production, especially variation at the low end of the distribution (non-conformities).

Costs to the Breeder

- DNA testing and analysis services
- Cost of breeding daughters back to their sires.
  - Losses due to affected progeny
  - Loss(?) of potential value of unaffecteds due to inbreeding

Value of the Inbred Progeny

- Are inbred animals worth more or less than non-inbred animals from similar families?
  - Are unaffected inbred animals more or less likely to carry a genetic defect than outbred animals?

Value of the Inbred Progeny

- Are inbred animals worth more or less than non-inbred animals from similar families?
  - Are unaffected inbred animals more or less likely to carry a genetic defect than outbred animals?
    - **Less likely, because the affected animals have been removed.**

Value of the Inbred Progeny

- Are inbred animals worth more or less than non-inbred animals from similar families?
  - Are unaffected inbred animals more or less likely to have extremely high genetic merit?

Value of the Inbred Progeny

- Are inbred animals worth more or less than non-inbred animals from similar families?
  - Are unaffected inbred animals more or less likely to have extremely high genetic merit?
    - **More likely, because the genetic variance of inbred progeny is greater than that of outbred progeny.**

Value of the Inbred Progeny

- It really is a matter of how effectively you can market them.
- There should be good opportunity for really creative marketers.

Standard Operating Procedure

- The benefits of this approach would increase substantially if it ever became routine for sires that were to become influential in their breeds.
- Eventually, most sires to be tested would have pedigrees that consisted primarily of previously tested sires.
  - This would decrease the number of defects present in those sires
  - It would also make the mapping of defects in those sires more efficient.

Paradigms for Managing Recessive Defects

- Don't restrict registration of known carriers
  - Unnecessary, self-imposed tax on breeders
- Myth that defects replicate like viruses
  - There rarely is strong selection for carriers of recessive defects.
- Use mating systems to avoid mating carriers to each other.

Do You Want to be Reactive or Proactive?

- The current approach to managing genetic defects by putting out fires is reactive.
- The approach I am proposing here is proactive, but comes with extra cost, especially initially.

Conclusions

- A mating system for systematically detecting and selecting against recessive defects may be feasible.
  - It may improve uniformity and reduce nonconformities, but the extent to which it would be effective is unknown.
  - This mating system would require a new class of DNA testing services that is not currently commercially available.
- This is an application of DNA testing that has been relatively unexplored.