A "genetics first" approach to selection

Gary L. Bennett, Warren M. Snelling, and Tara G. McDaneld

USDA, US Meat Animal Research Center

Clay Center, Nebraska, USA

Agricultural Research Service

Livestock Genomics

Mutation Load, Mode of Action

Inbreeding & Heterosis

Presentation Outline

Part 1

Presentation Outline

Part 2

Livestock Genomics

Mutation Load, Mode of Action

Inbreeding & Heterosis

Hypothesis

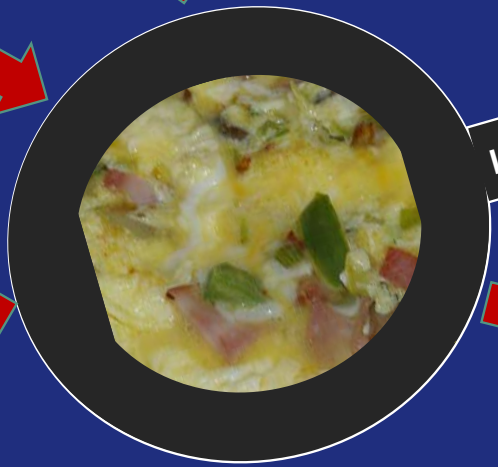
Presentation Outline

Part 3

Livestock Genomics

Mutation Load, Mode of Action

Inbreeding & Heterosis



Hypothesis

Livestock limitations to selection

Tes

Mutation Load and Mode

- Muller (1950) "Our load of mutations" determined that at equilibrium
  - Effect of mutation on population mean = frequency × allele effect
  - Frequency of a mutation is inversely proportional to its effect size
  - Population effect of a mutation is independent of the size of its effect

- Kaczer & Burns (1981) "The molecular basis of dominance" determined that mutations
  - Are likely to be recessive due to kinetics of pathways
  - Are likely to have smaller effects

- *Relevant points*
  - Many mutations are likely to have small effects, be recessive, and have higher frequencies resulting in moderate effects on a population basis

Inbreeding and Heterosis

- Dickerson (1973) "Inbreeding and heterosis in animals"
  - Broadly related performance of inbred lines, pure breeds, and their crosses on the same continuum of inbreeding relative to breed crosses
  - Summarized the difficulty researchers in the 1930's through 1960's experienced trying to overcome inbreeding depression by selection
  - Noted the generality of heterosis between unrelated populations and inbreeding depression within populations
  - Pointed to heterosis for fertility and for cumulative traits

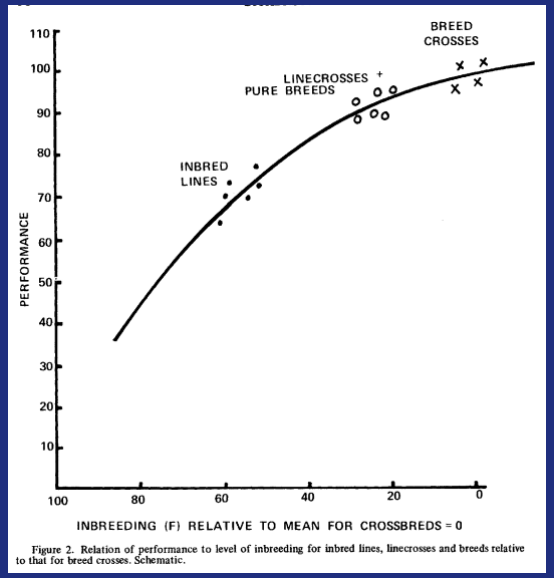


Figure 2. Relation of performance to level of inbreeding for inbred lines, linecrosses and breeds relative to that for breed crosses. Schematic.

- *Relevant points*
  - Heterosis and inbreeding depression likely due to many variants with small effects
  - Largest effects on traits where timing of physiology (fertility) and regularly repeated performance (lifetime productivity) are important, i.e., small deviations in a few components could have large consequences

Livestock Genomics

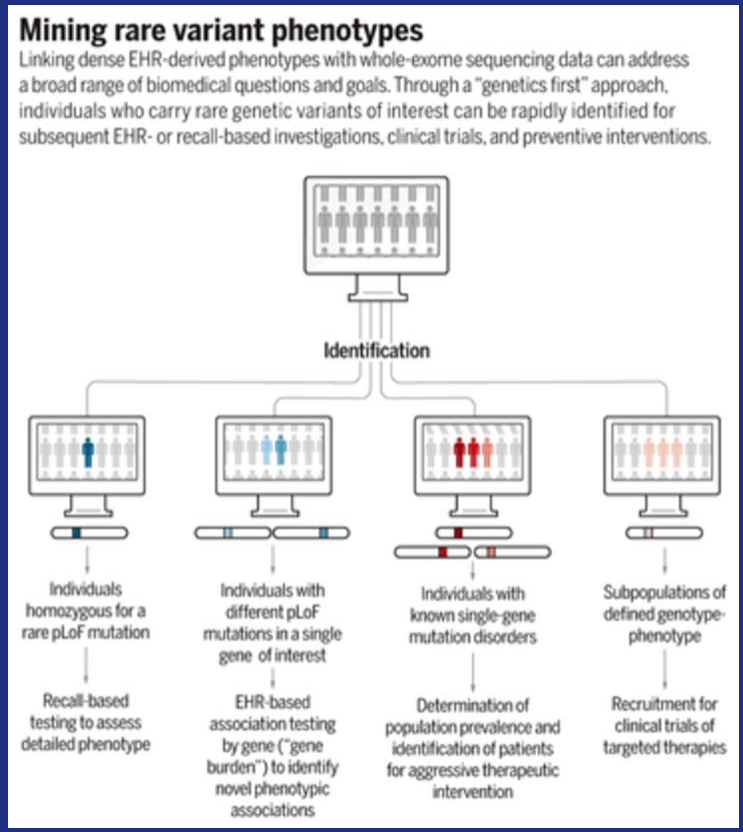
- Snelling *et al*. (2015) "A survey of polymorphisms … (15) popular beef breeds"
  - 83,379 non-synonymous, 69,103 regulatory, and 5,153 loss of function (LOF) variants
  - Typical bull has about 900 LOF variants
  - ~30% LOF shared by many breeds; ~5% LOF unique to a specific breed
- Many of the OMIA "Defects" with known DNA variants are loss of function
- Mesbah-Uddin et al. (2017) found QTL for health and reproduction near deletions
- Specific LOF alleles have been identified with low fertility
- Genotyping panels are widely used and new and modified panels are being introduced
- Some LOF are good – disease vector receptors

- *Relevant points*
  - Functional animals have many LOF variants -- possibly small effects and recessive
  - LOF variants do seem more likely to affect some phenotype

Genomics Trend

- "Reverse genetic screen" & "Genetics first" approaches

- *Human example from Dewey et al. (2016) Science article*
  - Begins with very large exome sequence and health records database
  - Identifies people with homozygous, rare LOF
  - Examines their health records



Livestock Limitations to Genomic Selection

- Current genomic selection needs continuous
  - Genotyping
  - Phenotyping
  - Training in large populations of closely related animals

- *Relevant points*
  - Limited to large population
  - Limited to phenotypes readily measured on many animals

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Hypothesis

- Loss of function variants have an accumulative effect on some traits, especially fitness and reproductive traits and having fewer LOF variants will improve those traits

- *Advantages IF TRUE*
  - Could be applied to many populations without training
  - Could improve traits that are less easily phenotyped and recorded

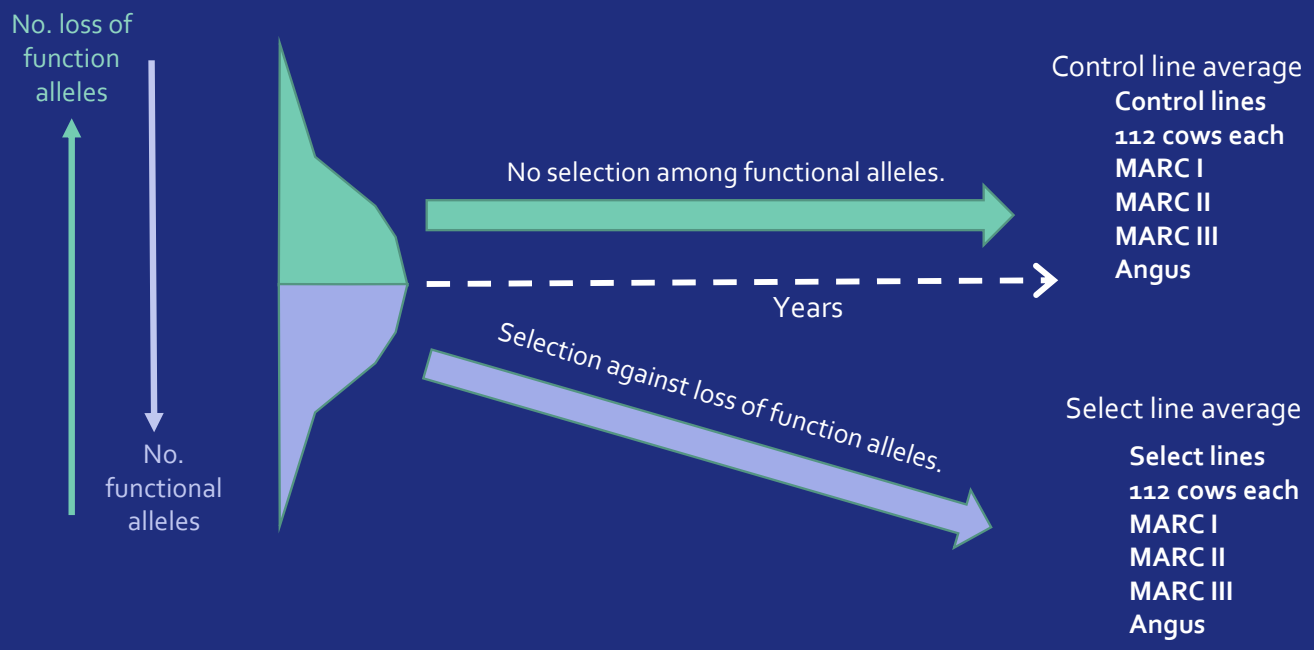
GGP F250 functional genotyping

More putative LOF than Snelling discovered in 270 bulls: 8,000 vs 5,000

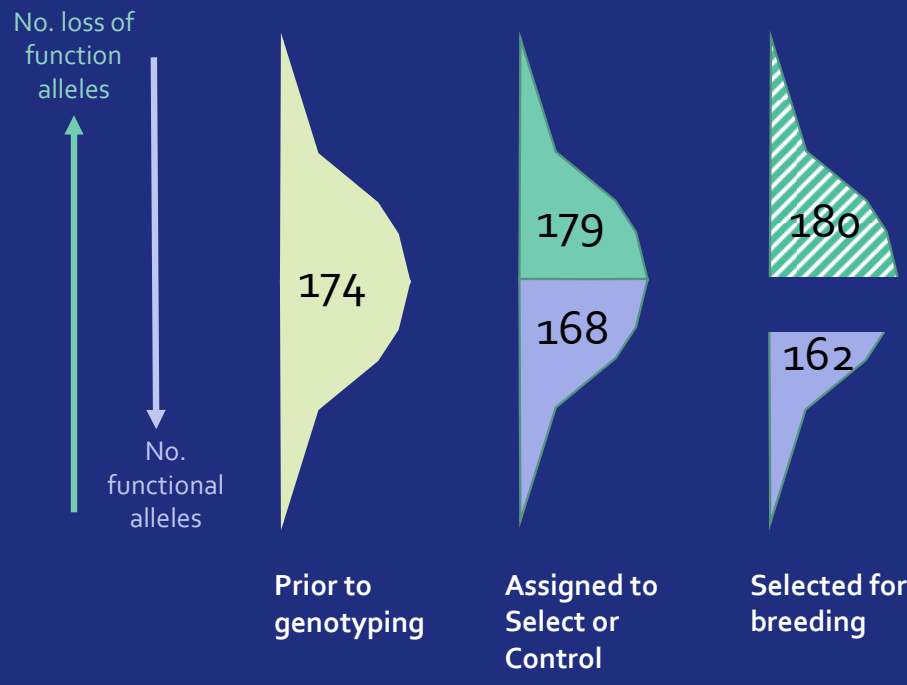
But many markers are monomorphic in our cattle: ~700 segregating

Overall putative LOF allele counts are much less with F250

Experiment: Selecting Functional Alleles (SFA)



Experiment: Heifers born in 2017



Control line average

Control lines
30 heifers each
MARC I
MARC II
MARC III
Angus

Select line average

Select lines
30 heifers each
MARC I
MARC II
MARC III
Angus

Other thoughts

- Sequence would identify more LOF than genotyping panels
- Improving annotation and molecular modeling could identify other types of variants with high probability of affecting traits
- Weighting selection by probability of predicted molecular effect or by degree of segregation distortion might improve response