A “genetics first” approach to selection

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Presentation Outline

Part 1

Livestock Genomics

Mutation Load, Mode of Action

Inbreeding & Heterosis
Presentation Outline

Part 2

Livestock Genomics

Mutation Load, Mode of Action

Inbreeding & Heterosis

Hypothesis

Livestock limitations to selection
Inbreeding & Heterosis

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Livestock Genomics

Presentation Outline

Part 3

Hypothesis

Livestock limitations to selection
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

- 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

  - 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)

- Control line average
  - Control lines
  - 112 cows each
  - MARC I
  - MARC II
  - MARC III
  - Angus

- Select line average
  - Select lines
  - 112 cows each
  - MARC I
  - MARC II
  - MARC III
  - Angus

- No selection among functional alleles.
- Selection against loss of function alleles.
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

- Prior to genotyping: 174
- Assigned to Select or Control: 179
- Selected for breeding: 180

- No. loss of function alleles
- No. functional alleles
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

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