


**IDENTIFICATION AND MANAGEMENT OF ALLELES
IMPAIRING HEIFER FERTILITY WHILE
OPTIMIZING GENETIC GAIN IN ANGUS CATTLE**

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Background & Rationale

- **Long-term goal:** Improve the reproductive rate of US beef cattle within the context of selection to improve overall profitability to the herd
- Improvement of reproductive efficiency of the US beef herd...
 - Requires an integrated, systematic effort involving research and extension scientists in partnership with industry stakeholders and commercial cattle producers



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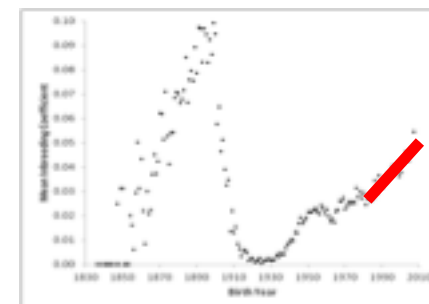
Background & Rationale

- Productivity and sustainability of beef production are dependent upon maximizing the number of females that conceive early in the breeding season.
- Angus breed accounts for ~ 70% or more of genetics in US beef production systems (likely to increase)
- Increased use of AI in the Angus breed has resulted in a reduction in diversity due to a narrowing of the genetic base



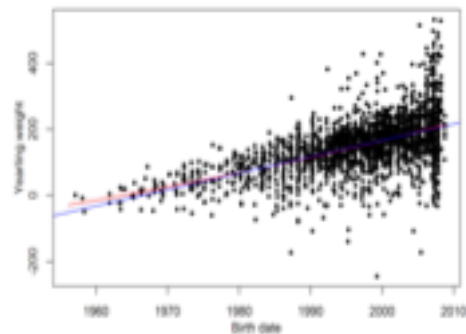
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Mean inbreeding coefficients by birth year for 76,083 Angus animals forming a 64 generation pedigree including 3,570 genotyped animals. Effective population size ($N_e = 116.15 \pm 0.04$) was estimated for animals born ≥ 1980 .

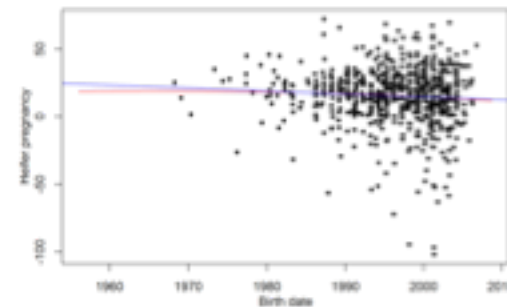


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Deregressed EBVs for Yearling Weight of 2,755 registered Angus bulls demonstrates that breeders have achieved an average increase of 4.96 lb per year (blue line) over a 50 year period.



Deregressed EBVs for Heifer Pregnancy Rate for 698 registered Angus bulls indicates that either as a correlated response to selection for production or due to accumulated inbreeding, Angus female fertility has decreased by 0.22%/per year for about the last 25 years.



Background & Rationale

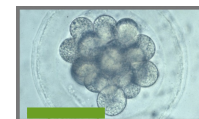
- Accumulation of inbreeding leads to homozygosity of alleles that reduce fitness (reproduction and survival)
- Homozygosity of alleles with deleterious effects on development or survival increases the overall probability of embryonic and early developmental lethals
- Presumably calves that are homozygous for a loss of function (LOF) allele will abort, be born dead, die soon after birth, or will never be observed in live animals thus inferring that the allele is lethal



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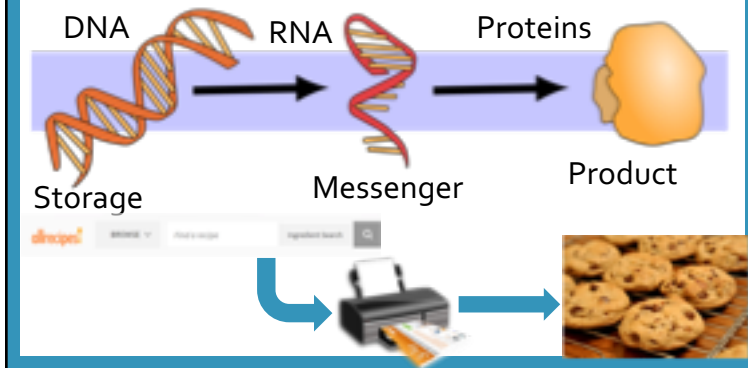
Project Goals and Background

- Tremendous gains in other production traits
 - Haven't seen these same gains in fertility-related traits
- No secret that reproduction is a very important trait in the cowherd
 - Improve reproductive rate in US beef cattle
 - Does not sacrifice performance in other ERT
 - Improves overall profitability of the cowherd
- 2 ways to increase fertility:
 - Maximize number of females that conceive early in the breeding season
 - Maintain pregnancies that are achieved

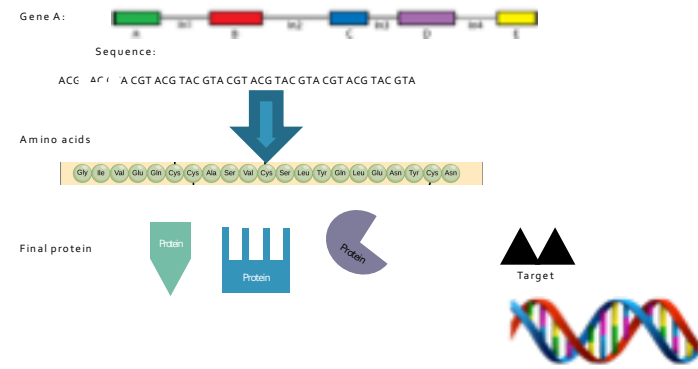


How can Genetics Impact Fertility?

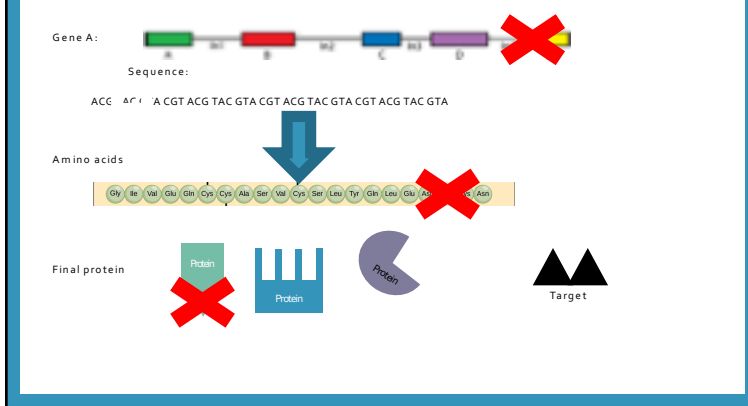
- Let's review the basics of genetics



When Things Go Right



When Things Go Wrong



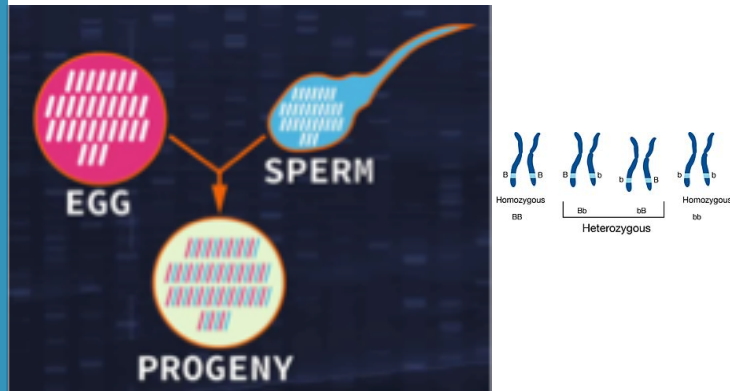
Broken Genes

- Broken genes can be a major problem
- Some genes are essential for life
- Basically-you don't have a functional copy of that gene, you die

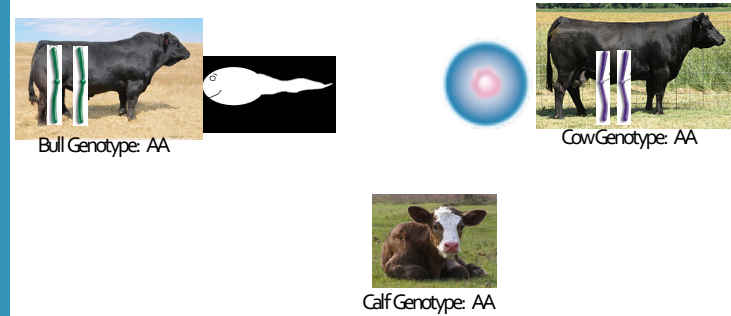
- 2 chances to get a functional copy (2 chr)



Each Parent Contributes an Allele



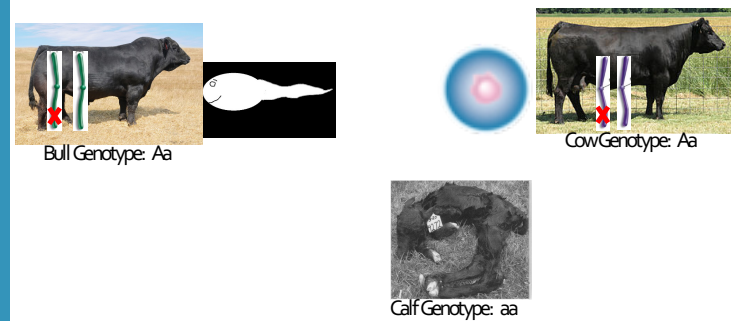
When all goes well....



When we have carriers....



When we have 2 carriers....

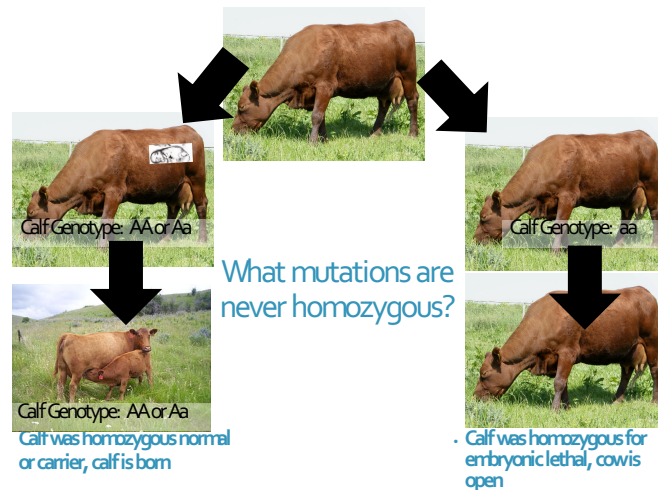


- Why do lethal alleles matter?
 - All have seen effects of other lethal alleles (AA, NH, TH, etc.)
 - Managing matings to avoid affected calves is good for profit and good for welfare
- Also have early embryonic lethals
 - Same concept, never see
 - Open cows, slower to breed back, abort and come back into heat
 - When the gene is needed for development, development stops, the cow fails to conceive/aborts, comes back into heat

The diagram illustrates the stages of bovine embryo development, showing the progression from fertilization to birth. The stages are represented by images of embryos at different developmental points, connected by blue arrows indicating the timeline.

- Pro-nuclear stage (hours after fertilization):** Shows two cells, each with a visible nucleus, under a microscope.
- Bovine blastocyst (day 7):** Shows a spherical cluster of cells with a central cavity, representing the blastocyst stage.
- Day 25 bovine embryo:** Shows a long, thin, translucent embryo with a visible head and tail region.
- Day 33 bovine embryo:** Shows a more developed embryo with a distinct head and tail, and a visible internal structure (indicated by a red arrow).
- 60 days:** Shows a small, pinkish, pig-like embryo next to a ruler for scale.
- 100 days:** Shows a larger, pinkish, pig-like embryo next to a ruler for scale.
- 120 days:** Shows a large, pinkish, pig-like embryo next to a ruler for scale.

Pictures courtesy of Dr. David Grieser



- 1. Sequence genomes of a large number of animals
 - Which mutations are never homozygous in live animals?
 - Which have large predicted changes in protein structure?
 - Which have been shown to be in genes essential for life in other species?




Table 1

Species	No. individuals	No. V-Loci Reads	Total Reads	Av. Read Coverage
Anguilla	100	62,367,357,368	1,377,364,080,718	22.78
Alboreus	10	17,049,177,049	1,391,196,763,617	26.76
Alburnus	10	3,769,149,619	357,334,483,249	18.27
Channa	10	8,939,127,059	659,475,779,267	21.54
Ctenopharyngodon	10	6,902,760,262	601,498,477,367	27.76
Glyptothorax	8	6,569,956,099	633,476,103,639	27.51
Hemibarbus	8	4,684,178,177	601,667,124,013	27.83
Heterobranchius	10	601,544,762	89,868,666,666	7.73
Hududius	2	1,849,487,482	143,361,277,893	24.89
Red Anguilla	10	6,435,070,149	601,348,088,499	26.89
Silurilabeo	10	12,019,602,249	1,396,354,882,760	9.52
Amur	8	1,399,479,992	159,479,992,760	8.63
Wuchang	10	759,127,128	75,494,494,494	2.54
Wuchang	10	1,875,487,482	187,775,487,482	7.24
Salmo	8	1,048,048,048	101,758,018,128	5.16
Salmo	8	1,363,737,249	1,874,869,053,736	9.67
Salmo	8	8,375,192,048	839,867,082,198	29.43
Carassius	132	96,911,894,912	1,634,911,894,912	22.87

Table 2

Species	No. individuals	No. V-Loci Reads	Total Reads	Av. Read Coverage
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How Do We Detect And Test If Variants Are Lethal?

- 2. Take the mutations from step 1 (candidates) and build a genotyping chip
- 3. Validate the candidate mutations
 - Genotype a large number of animals on the chip
 - 11,506 (mostly Angus) heifers genotyped
 - 18,271 animals total on the chip
 - Which candidates are still not seen as homozygous?



GGPF250



The Future

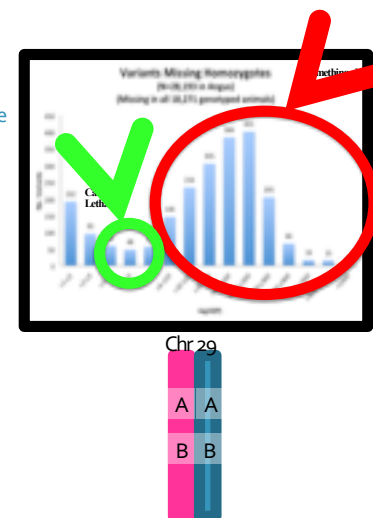
- Candidates can be placed on commercial genotyping assays
 - Important step!
- Ongoing process
 - New candidate mutations discovered and added to genotyping assays as more animals sequenced
 - Old candidates eliminated as more animals are genotyped
 - Find a homozygote
 - Hard to find homozygous animals for mutations at very low frequency in the population

Limitations of this Approach

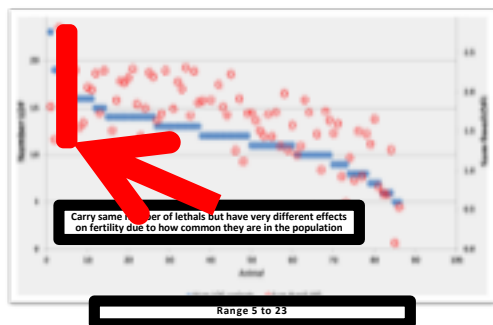
- Limited by the number of animals that have been sequenced
 - If not sequenced, may miss rare variants they possess
- Looking for variations in genes
 - Miss anything that may be important but not in a gene (the majority of the genome)
 - Regulate gene expression
- Dependent on the quality of the genome sequence
 - Missing genes or portions of genes
 - Improving the sequence assembly improves ability to ID variants in genes/functional variants
 - This was just done!

The Next Steps

- Narrow down and identify candidate lethal mutations
 - 2,224 candidates
 - Cannot all be lethal
 - This sounds like bad news, but it's great news
 - You can manage it if you know about it!
- Hopefully, incorporate into commercially available genotype tests
- Continuously-evolving process!
- How do we use this information?
 - Needs perspective



How Important is a Mutation?



How Can The Beef Industry Use This Information?

- Develop sector-level economic effects of increasing reproductive rates.
 - Using a structural econometric model of the US cattle sector, this portion of the project would provide a value to the expected increase in pregnancy rate that would result through investigation of recessive developmentally lethal alleles.



Dr. Scott Brown
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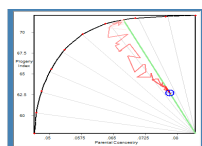
- Develop selection indexes that support multi-trait selection, inclusive of fertility traits
 - Develop selection indexes that incorporate fertility of females (including heifers) in the context of cow-calf and feedlot production with quality and yield grade based marketing of beef



Dr. Mike MacNeil
Delta G

How Can The Beef Industry Use This Information?

- Develop decision support software to optimize breeding schemes via implementation of selection indexes and mate selection based on size and dam recessive lethal genotypes
- Develop software to handle the mutations discovered in this project, and deliver selection and mating recommendations to US beef breeders that exploit this information optimally in competition with other factors of importance (e.g. trait merit, genetic diversity (inbreeding), genetic defects and recessive lethals, logistical constraints, semen costs, etc.)



Dr. Alison Van Eenennaam
Professor
University of California-Davis



Dr. Brian Kinghorn
Emeritus Professor
University of New England

To Learn More:

- Beefreproduction.org



Videos



Acknowledgements

- Breed Associations co-sponsoring sequencing:
 - American Angus Association
 - Australian Angus Association
 - Argentine Angus Association
 - American Hereford Association
 - Beefmaster Breeders United
 - American Gelbvieh Association
 - American International Charolais Association
 - American Simmental Association
 - American Maine-Anjou Association
- 10,000 heifers
 - Missouri Show-Me-Select Replacement Heifer Program
 - Missouri Angus Association
 - Circle A Angus
- USDA NIFA grants:
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- GeneSeek for building the GGP-F250



➤ Website: <http://beetereproduction.org>

Questions?

