Managing Genetic Abnormalities

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Range Beef Cow Symposium 2009
Casper, WY
December 1, 2009

background

- most genetic defects are going to have recessive patterns of inheritance
  - not problematic if present at a low allele frequencies
  - commercial cross-breeding programs have less risk
- recognition of genetic defects typically occurs after it is “too late”
- preventive management is necessary to reduce potential economic loss

recessive inheritance

female parent gametes \ male parent gametes	A	a
A	AA 25%	Aa 25%
a	Aa 25%	aa 25%

- a mating using two carrier (Aa) parents
- 25% affected offspring produced
- 50% carrier offspring – normal phenotype
- 25% normal offspring

issues

- changes in management and technology over the past two decades have significantly changed breeding programs
  - intensity of selection has increased
  - reproductive technologies insure widespread dissemination of high genetic merit animals
- coming changes may exaggerate the issues even greater
  - selection for specific genomic segments based on DNA technologies

options

- ignore it
  - deny it exists and hope it will go away
- complete elimination of genetic source
  - pedigree analysis insufficient
  - contrary to overall breed improvement
- find outcross genetics
  - breed away from it
- accurate identification of carriers combined with breeding management
  - how?

solution

- new genomic technologies insure rapid solutions to emerging problems
  - short- to mid-term time frame for the identification of causative genes/mutations
    - development of DNA-based tests
      - assembly of sufficient material = short-term success
      - high accuracy
      - cost effective
  - breeding decisions assisted by molecular tools
    - potential for elimination of deleterious mutation without loss of valuable germplasm

proof of principle

- solutions provided for several genetic defects provided in the past 5 years
  - tibial hemimelia (TH)
  - pulmonary hypoplasia with anasarca (PHA)
  - idiopathic epilepsy (IE)
  - dilutor (DL)
  - arthrogryposis multiplex (AM)
  - hypotrichosis (HY)
  - osteopetrosis (OS)
  - neuropathic hydrocephalus (NH)
- industry uptake of technology has been high

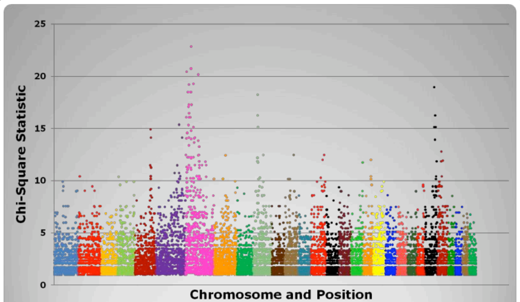
an example

- neuropathic hydrocephalus (NH)
  - first reports coincide with affected AM calves
  - invariably lethal
    - absence of CNS tissue
    - generalized hydrocephalus
    - skull malformation
    - mild arthrogryposis
- recessive inheritance
  - possible early embryonic death

experimental approach

- 6 affected calves
  - all with confirmed veterinary pathology
  - all parent verified
- 10 "control" samples
  - common ancestor
  - 9 selected for absence of putative common ancestor
- analysis on the Illumina BovineSNP50 Genotyping BeadChip

statistical analysis



outcomes

- localization to 6.6 Mb interval
  - rapid identification of associated marker haplotype – less than 2 weeks from sample collection
  - population screening identifies individuals with IBD haplotype except mutation
- resequencing of genes within region for known genotypes
- single SNP identified

how accurate are the tests?

- two major components to accuracy
  - scientific basis and testing process/execution
- tests are based on specific mutations associated with each genetic defect
  - tests do not use "linked" or "associated" changes in the DNA
- testing process starts at sample collection and ends at reporting

scientific support

- non-synonymous substitution in conserved functional domain
  - bacteria, fungi, plants and vertebrates
- mouse “knockout” results in 100% fetal mortality
  - pronounced irritability and hyperactivity in heterozygotes
- proband’s parents are homozygous for normal allele
- genotype frequency in living animals
  - 830 heterozygotes, 3378 homozygous normal

emerging issue

- Fawn Calf Syndrome (FCS)
  - semi-lethal
  - joint laxity/contractures
    - connective tissue
  - poor muscle development

- recessive inheritance
  - confirmed by WGA/ homozygosity analysis
  - 17 calves – 2 Mb interval
- gene and mutation identified
  - still “perfecting” an accurate DNA test

where to implement

- differs based on place in production system
  - seedstock
    - increased responsibility/liability
    - highest management(?)
  - commercial with replacement
    - commitment to manage female base
  - commercial terminal
    - little or no risk with genetically free bulls

what is my risk?

- decrease risk with increase in generations
  - $(1/2)^n$ = probability of carrier
    - n = number of generations between known carrier and individual in question
  - 1 generation = ½ = 50%
  - 3 generations = ½ x ½ x ½ = 12.5%
  - 7 generations = ½ x ½ x ½ x ½ x ½ x ½ x ½ = 0.8%
- individual breeder decides acceptable risk
  - how much risk are you comfortable with?

cost management

- expense vs. outcome
  - low cost – no affected calves born
    - sires only – no affected calves born to genetically “free” sires
  - moderate cost – on the road to elimination
    - sires, herd matriarchs and annual replacement heifers
  - highest cost – complete management
    - all animals in the herd
      - does not imply elimination, only management

should I use carrier animals?

- are there other defect-free animals with equal genetic value?
- is it worth the $$/opportunity cost?
- is your management good enough?
- what is the purpose of retaining carriers?
- how important is it to eliminate defects from the population?

recessive inheritance

male parent gametes

female parent gametes	A	A
A	AA 25%	AA 25%
a	Aa 25%	Aa 25%

- a mating using at least one free (AA) parent
- free parent can only produce A gametes
- no affected offspring produced
- 50:50

summary

- genetic abnormalities have the potential to cause significant economic loss
- with new genomic technologies, solutions can be very rapid
  - genetic defect research should be viewed as "preventative" investment
  - must have a proactive and positive attitude toward defect surveillance and reporting
- we can make the management tools, you can decide how to use them
  - education is the key

acknowledgements

- Brandy Marron, MS
- Stacey Meyers, PhD
- Alysta Markey, MS

- University of Nebraska Lincoln
  David Steffen, DVM, PhD

- USDA MARC
  Tim Smith, PhD
- USDA BARC
  Tad Sonstegard, PhD

- University of Missouri
  Jerry Taylor, PhD

- Interested and proactive breeders

- American Angus Association
- American Hereford Association
- Red Angus Association of America

- USDA/CSREES and USDA/ARS