DNA Tools for Managing Genetic Defects

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production values

- often motivated to increase output
  - more or better product = more $$$
- shift toward reduction of inputs or optimization of production systems
  - less input, same output = more $$$
- decreased losses also need consideration
  - increased genetic defect frequency = potential loss = less $$$

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"
  - allele frequency is sufficiently high to cause consistent frequency of affected calves
  - threat proportional to population size

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 4 years
  - tibial hemimelia (TH)
  - pulmonary hypoplasia with anasarca (PHA)
  - idiopathic epilepsy (IE)
  - arthrogryposis multiplex (AM)
  - hypotrichosis (HY)
  - osteopetrosis (OS)
  - neuropathic hydrocephalus (NH)
- industry uptake of technology has been high

an example

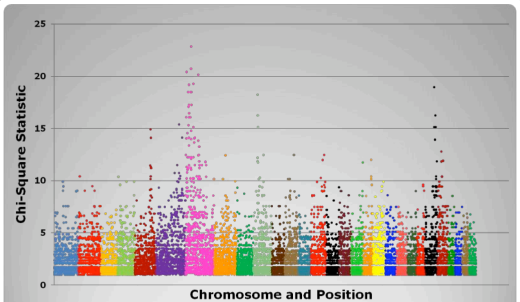
- neuropathic hydrocephalus (NH)
  - first reports coincide with affected AM calves
  - invariably lethal
    - absence of CNS tissue
    - generalized hydrocephalus
    - skull malformation
    - mild arthrogryposis

- putative recessive inheritance
  - unclear due to prior heightened awareness of AM pedigrees

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

further 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
    - neurological
    - connective tissue
- recessive inheritance
  - confirmed by WGA/ homozygosity analysis
  - 12 calves – 3 Mb interval
- haplotype analysis shows low to moderate frequency

implementation

- differs based on place in production system
  - seedstock
    - highest management
  - commercial with replacement
    - commitment to manage female base
  - commercial terminal
    - little or no risk

breeding 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

required change

- education
- the psychology of breeders toward genetic defects
- industry wide standard reporting processes – reimplementation of “old” protocols
- central location(s) for establishing collections for DNA analysis

summary

- genetic defect research should be viewed as “preventative” investment
- solutions can be very rapid
- must have a proactive and positive attitude toward defect surveillance and reporting

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