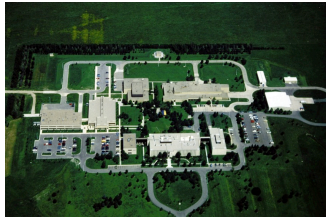


USMARC Symposium at BIF: 50 Years of Service to the Beef Industry

June 18, 2014



Steven Kappes
USDA-ARS Deputy Administrator, Office of National Program

The Genomics Era From Whence it Came



Genetics and Biochemistry

- Theoretical Population Genetics 1920-1930s (Wright, Fisher, Haldane)
- Selection Index, Breeding Values 1940s (Hazel, Lush)
- Mixed models, BLUP 1950-1960s (Henderson)
- Heterosis 1970s (Cundiff, Dickerson, Gregory)
- Application of BLUP theory to field data 1980s (Van Vleck, Willham, Quaas and Pollak)
- Nucleic acid- hereditary information 1940s (Avery, MacLeod, and McCarty)
- DNA Structure 1953 (Watson and Crick)
- PCR 1986 (Mullis and Faloona)

We are standing on the shoulders of giants!!!!

The Genomics Era in the Early Days

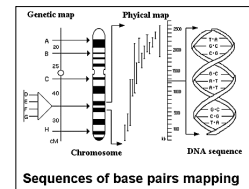
Genetic Markers

- Blood Groups- Erythrocyte Antigens, Serum Proteins
 - Blood Typing Labs (\$35/animal for parentage)
- Restriction Length Polymorphisms (RFLP)
 - Detected by restriction enzyme that cuts DNA at a certain sequence **GAATTC**
- Microsatellites 1985 (1990s- cost \$1/genotype)
 - allele 1 **GCTACACAGTCC**
 - allele 2 **GCTACACAGTCC**

The Genomics Era in the Early Days

The first cattle genetic maps

- Cytogenetic Maps
- Physical maps
 - Radiation Hybrid Maps (Synteny Groups)
 - Fluorescence in Situ Hybridization (FISH)
- Linkage Maps
 - Only need 150 markers
 - 1994 (Bishop, Barendse)

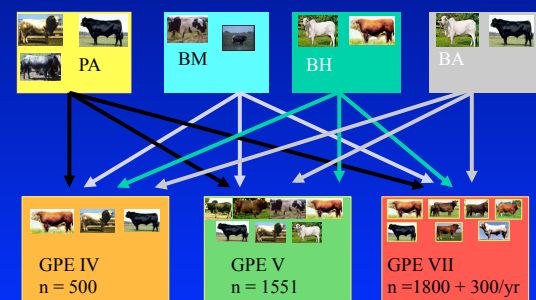


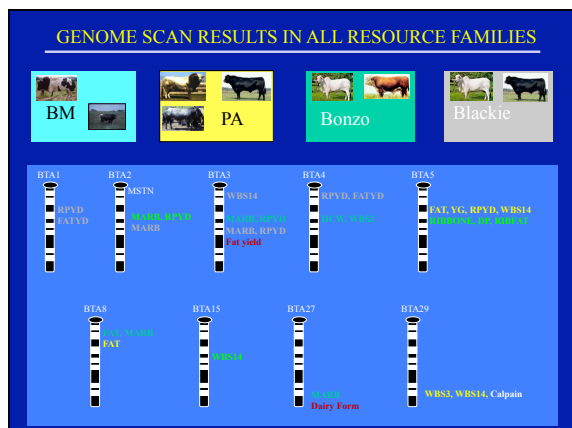
Genomic Research

- Develop road maps of each chromosome (genetic linkage maps)
- Utilize linkage maps to identify chromosomal regions
- 'Fine map' the region to identify the gene



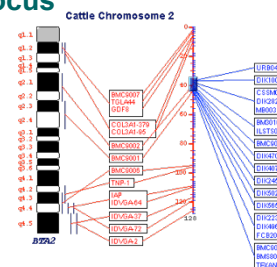
Characterization of QTL variation in resource populations





Using the Linkage Map for Fine Mapping a Locus

- Linkage map
 - Relative location
- Allows use for QTL mapping



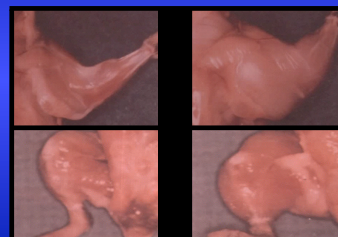
Piedmontese Myostatin Allele

						C313Y					
	Tyr	Cys	Ser	Gly	Glu	Tyr	Glu	Phe	Val		
Piedmontese	tac	tgc	tct	gga	gaa	tAt	gaa	ttt	gta		
Normal	tac	tgc	tct	gga	gaa	tGt	gaa	ttt	gta		
	Try	Cys	Ser	Gly	Glu	Cys	Glu	Phe	Val		
						Amino acid 313					



Double Muscling is Caused by Inactivation of Myostatin (MSTN)

Normal mstn (-/-) knockout



Nature 387:83-90, 1997

Cattle genes affecting carcass traits

- Thyroglobulin- marbling (Gene Star)
- Somatostatin- marbling
- Calpastatin- tenderness (Gene Star)
- Calpain- tenderness
- Leptin- fat deposition
- DGAT- milk fat

Limitations in genomic research (2003)

- Single gene (marker) selection is worse than single trait selection
 - Need to incorporate with EPDs
- We need to rapidly identify sufficient number of genes that explain the majority of the genetic variation
 - Need additional laboratory tools and technology
- Animal Genomics Motto-
 - We need more markers, we need more animals

Cattle Genomics

Still need More DNA Markers

- We need to sequence the Bovine Genome!!!! (1998)
 - Sequencing the Human Genome \$100M
 - Public and Private efforts
 - Published 2001
- Newer version of a Cattle Physical Map
 - Bacterial Artificial Chromosome (1999)
 - Call from Dan Laster
 - Prerequisite for sequencing the genome
 - International effort- Line 1 Hereford
 - Holstein (Monsanto)
- Alliance for Domestic Animal Genomic Research (Kelly Eversole), Animal Agriculture Alliance
- 2002 National Academy of Science Workshop
 - The time is right to sequence farm animals



Cattle Genomics

Sequence the Bovine Genome

- NHGRI call for proposals
 - Baylor College of Medicine
 - Milk and Honey Meeting 2000



L1 Dominette 01449

Bovine Genomic Sequencing Initiative Cattle-izing the Human Genome

Richard Gibbs and George Weinstock, Baylor College of Medicine, Human Genome Sequencing Center; Steven Kappes, USDA-ARS, US Meat Animal Research Center; Lawrence Schook, University of Illinois; Loren Skow and James Womack, Texas A&M University

Interagency Coordination Essential....

Interagency Working Group on Domestic Animal Genomics

- Executive Office of the President
 - Office of Science & Technology Policy (OSTP)
 - NSTC Committee on Science (co-Chairs NIH, NSF, OSTP)
- Charter members (Established in 2002)
 - DOE, FDA, NIH, NSF, OMB, OSTP, USDA
- Chairperson -- Joseph Jen, USDA/REE
- Executive Secretary -- Ronnie Green, USDA/ARS
- USDA Animal Genomics Workshop 2005
- Blueprint for USDA Efforts in Animal Agriculture Genomics
 - Words of Wisdom-



Inclusion of molecular genetic information into breeding value prediction and mating system design will require new approaches, not the least of which is the ability to handle large volumes of data with efficient computing algorithms (Green 2007).

International Collaboration

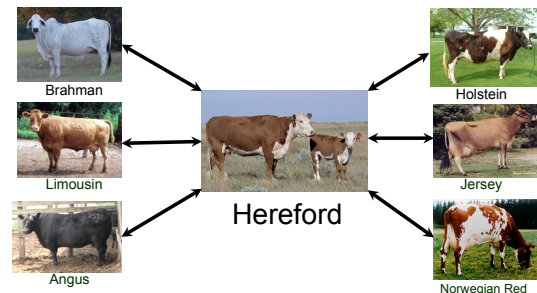
- 2003 Baylor College of Medicine started the \$53 Million Bovine Genome Sequencing Project (NIH will pay 50%)
- 50% Matching Funding Provided By:
 - USDA Cooperative State Research, Education and Extension Service (CSREES) & Agricultural Research Service (ARS)
 - The State of Texas
 - Genome Canada
 - The Commonwealth Science and Industrial Research Organization of Australia
 - Agritech Investments Ltd., Dairy Insight Inc and AgResearch Ltd of New Zealand
 - Robert J. Kleberg, Jr. and Helen C. Kleberg Foundation
 - National, Texas and South Dakota Beef Check-off Funds

Phase II of the Sequencing Project

- International Scientific Community Assembled:
 - 306 investigators from 108 institutions/locations (Sequence)
 - 90 investigators from 40 institutions/locations (HapMap)
- Discovery of new genetic markers
 - Single Nucleotide Polymorphisms (SNP)
 - gga gaa tA t gaa
 - gga gaa tG t gaa
 - Development of faster and cheaper genotyping platforms
- Full Length cDNA clones (genes)
 - Expressed Sequence Tags (EST)

Phase II- SNP Discovery

Expect 3 Million SNP in the genome



Phase II - SNP Project

Bovine HapMap Consortium

- **Current Status of Project:**
 - Industry invited to assist in funding SNP validation \$1000/animal (Goal 20K SNP)
 - Genotyping completed on total of ~500 animals (19 breeds) for total of 40K SNP
 - Breeds include: Angus, Hereford, Limousin, Charolais, Red Angus, Piedmontese, Romagnola, Brahman, Santa Gertrudis, Beefmaster, Nellore, Gir, N'Dama, Sheko, Holstein, Jersey, Brown Swiss, Norwegian Red, Guernsey



Bovine 60K SNP chip is available

to 10,000 samples.

ETHUS: to Develop Bovine BeadChip, Plans to Market It in Early 2007

by David H. Ross, DVM, MS, PhD

ETHUS is a consortium of researchers from the University of Illinois, University of California, and the University of Georgia. The project is a collaborative effort to develop a high-density SNP chip for use in dairy cattle. The chip will be used to identify genes associated with important traits such as milk production, disease resistance, and reproductive performance. The project is funded by the National Science Foundation and the USDA.

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Bovine 750K SNP chip

to 10,000 samples.

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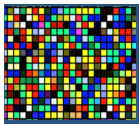
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Are 60K SNPs enough?

Cooperative Dairy DNA Repository- BARC

- >110,000 units of semen (~150K?)
 - >15 gallons!
- Holstein
 - 10,985 Bulls
 - 201 (115) families with at least 10 (25) sons
- Jersey
 - 556 Bulls
 - 17 (2) families with at least 10 (25) sons
- Guernsey
 - 160 Bulls
 - 2 families with at least 10 sons
- Brown Swiss
 - 177 Bulls

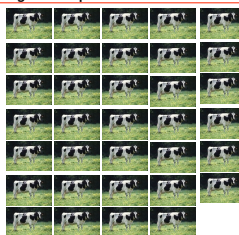


- Genome Wide Association Study

What is a SNP genotype worth?



Pedigree is equivalent to information on about 7 daughters



For the protein yield ($h^2=0.30$), the SNP genotype provides information equivalent to an additional 34 daughters

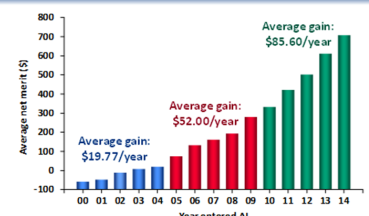
What is a SNP genotype worth?

And for daughter pregnancy rate ($h^2=0.04$), SNP = 131 daughters



Progress in the dairy industry

Genetic merit of marketed Holstein bulls



Started to use 50K SNP chip in April 2008, most of the gains are from including low heritable traits into the Selection Index.

Current cost and rate of generating data

Cost of Sequencing (\$53M for 10X)

- 900 X coverage of the bovine genome in 10 days (\$149K)
 - \$166 per 1X coverage (usable sequence)
- 40X coverage in 29 hours for \$4100
 - \$102.50 per 1X coverage

Cost of Genotyping (over \$1/genotype)

- 750,000 SNP for \$185
 - 9.5 cents/genotype
 - Imputing genotypes and sequence

Time and cost to fine map a QTL

- Previous time and cost -1year and \$40,000 to 70,000
- Today 1.5 hours

What is the potential of Genetic Selection?

- The cost of generating genetic information will continue to decrease
 - Inclusion of lower heritable traits
 - Animal health- OPP, Scrapie, PRRS
 - BRDC
 - Reproduction- conception rate, stillbirth, calving ease
 - Efficiency- longevity
- Designing the cow for the environment and feed resources
 - DECI
- I know I can't predict the future but it will be exciting!



From Bakewell to BLUP to Genomic Enhanced EPDs

