


Gene Set Enrichment Analysis for Feed Efficiency in Beef Cattle



www.BeefEfficiency.org

H.L. Neibergs¹, J.L. Mutch¹, M. Neupane¹, C.M. Seabury², J.F. Taylor³, D.J. Garrick⁴, M.S. Kerley³, D.W. Shike⁵, J.E. Beever⁵, US Feed Efficiency Consortium³, K.A. Johnson¹

¹Washington State University, Pullman, WA; ²Texas A&M University, College Station, TX; ³University of Missouri, Columbia, MO; ⁴Iowa State University, Ames; ⁵University of Illinois, Urbana



THE PROJECT

- Dr. Jerry Taylor is the Project Director
- 5 Year/\$5M USDA NIFA-funded project
- Research Aims (related to this talk):
 - Develop a national genomic selection program for multiple beef breeds
 - Identify genes that are associated with feed efficiency



PARTICIPANTS

20 INVESTIGATORS 11 INSTITUTIONS



 Iowa State University Dr. Darrian Garrick Dr. Stephanie Hansen Dr. Dan Loy Dr. J.R. Tait	 Kansas State University Dr. Robert Schnabel Dr. Robert Weaber	 University of Nebraska Dr. Matt Spangler
 Texas A&M University Dr. Chris Seabury	 GeneSeek, A Neogen Company Dr. Daniel Pomp	 USDA-BELTSVILLE Dr. Tad Sonstegard
 University of Illinois Dr. Jon Beever Dr. Dan Faulkner Dr. Dan Shike	 USDA-MARC Dr. Harvey Freedly Dr. John Pollak	 Oes
 University of Minnesota Dr. Scott Fahrenkrug	 University of Missouri Dr. Jerry Taylor, Project Director Dr. Monty Kerley	 Washington State University Dr. Kris Johnson Dr. Holly Neibergs







OUTLINE

- Introduction
 - Why is feed efficiency important?
 - Measuring feed efficiency
- Materials & Methods
 - Animals & phenotypes
 - Genetic analyses
- Results & Conclusions


IMPORTANCE OF FEED EFFICIENCY

- 10% improvement in average daily gain increases profitability by 18%
- 10% improvement in feed efficiency increases profitability by 43% (assuming a 2 lb/day reduction in RFI)
 - Across the entire feedlot sector this would equate to a reduction of \$1.2 billion in feed costs





GENETICS AND FEED EFFICIENCY

- Breeds of cattle differ in their abilities to use dietary energy
- Considerable variation exists among individuals within a breed which would support selection for energy use efficiency
- In beef cattle, RFI is moderately heritable, and genetically independent of level of production (*Arthur et al., 2001; Lancaster et al., 2009*)



www.pinterest.com



WHY A GENOMICS APPROACH?

- Feed intake phenotypes are expensive to measure so the using of selection to improve feed efficiency is logical and cost effective
- Current genomic tools make genomic selection across breeds that are accurate and robust possible



PROBLEM

- Selecting for feed efficient animals requires that we have a good measure for identifying them
- What traits should we select for feed efficiency?
 - Dry matter intake
 - Average daily gain
 - Feed conversion rate
 - Residual feed intake

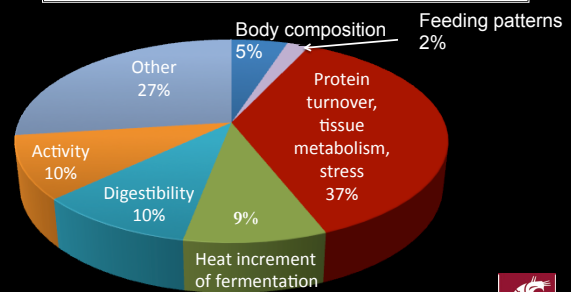


RESIDUAL FEED INTAKE (RFI)

- RFI is a measure of feed efficiency that quantifies the variance in feed intake *unrelated* to level of production (*BW and ADG in growing cattle*)
 - It may be a useful trait to use to examine the biological mechanisms associated with variation in feed efficiency
- Efficient animals (*negative RFI*) consume less feed than expected for a given BW and growth rate



BIOLOGICAL BASIS OF VARIATION IN RFI OF BEEF CATTLE



Herd and Arthur, 2009

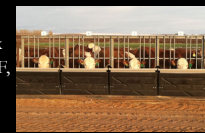


Animals & Phenotypes



HEREFORD CATTLE OLSEN RANCHES, HARRISBURG, NE

- DNA samples were collected on 847 Hereford cattle over a 3 year period (2009-2011)
- Date of birth (DOB), date of weaning, sex (S), breed composition, days on feed (DOF, min. of 70 days), feed intake (DMI) and weights were collected with a GrowSafe system
- 824 steers comprised 9 male contemporary groups and 23 heifers were in a single contemporary group



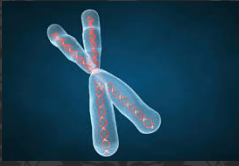

<http://www.olsenranches.com/feedtrials.html>

GrowSafe Feeding system at Olsen Ranches




RFI

- RFI was calculated by subtracting the expected DMI from the actual DMI
 - Low RFI – most efficient
 - High RFI – least efficient
- Expected DMI was calculated by incorporating covariates for average daily gain (ADG), mid-test metabolic weigh (MMWT), CG, S, DOB and DOF to estimate RFI


$$DMI = b_0 + b_1(ADG) + b_2(MMWT) + b_3(CG) + b_4(S) + b_5(DOB) + b_6(DOF) + Animal + e$$


GENETICS




GENOTYPES

- 489 Herefords were genotyped with the Illumina BovineHD BeadChip and 358 Herefords were genotyped with the BovineSNP50 BeadChip
- BovineSNP50 BeadChip genotypes were imputed with Beagle 4.1 to the density of the BovineHD BeadChip




www.farmflavor.com



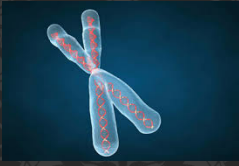

ANALYSIS

- Genome-wide association analysis was performed using GRAMMAR mixed model software in GenABEL (<http://www.genabel.org/>; Aulchenko et al., 2007)
- Most significant SNPs within 8 kb for 19,723 annotated genes in UMD 3.1 were selected as a proxy and used for Gene Set Enrichment Analysis (GSEA)
- 4,389 gene sets were taken from 5 databases: GO (3147), KEGG (186), Reactome (647), Biocarta (217) and Panther (165)




ANALYSIS

- Significance was calculated using the null distribution estimated from 10,000 permutations (Holden et al., 2008)
- Enrichment score was calculated for each pathway using a modified Kolmogorov-Smirnov statistic and normalized (NES) based on the size of each gene set.
- NES>3.0 were gene sets associated with RFI



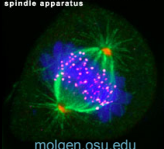
RESULTS




GENE ONTOLOGY

- GO:0005813 Centrosome(5) are cellular components critical in mitosis and meiosis, regulation of the cell cycle and stability of the genome
 - NES = 3.19, $p = 0.0010$
 - 99 genes in gene set, 37 leading edge genes
 - 15 of the leading edge genes were also enriched in cytoskeleton organization(4)

Centrosomes (red) and the mitotic spindle apparatus




molgen.osu.edu



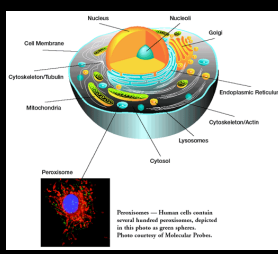
GENE ONTOLOGY

- GO:0007010 Cytoskeleton organization(4) is a component of biological processes. It consists of 246 genes; 97 were leading edge genes with RFI.
 - NES = 3.07, $p = 0.0011$
 - Leading edge genes are associated with tumor growth, obesity, feed efficiency traits in poultry (Kong et al., 2011) and in cattle (Rolf et al., 2012; Keogh et al., 2016)




KYOTO ENCYCLOPEDIA OF GENES AND GENOMES (KEGG)

- KEGG:04146 Peroxisome is part of cellular processes involved in cellular transport and catabolism. They are small organelles essential in free radical detoxification, lipid homeostasis and hydrogen peroxide metabolism that is critical in maintaining cellular membrane integrity and animal health.


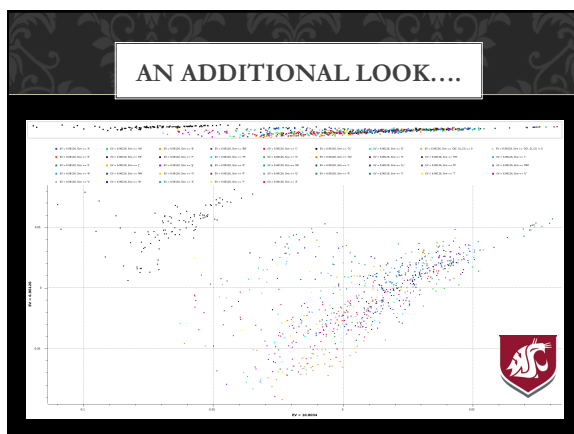


Peroxisomes — Human cells contain several hundred peroxisomes, depicted in this photo as green spheres. Photo courtesy of Molecular Probes.



PEROXISOME

- NES = 3.05, $p = 0.0016$
- There were 73 genes in the KEGG:04146 Peroxisome gene set and 30 of those were leading edge genes
- SOD1* was shared with GO:0007010 Cytoskeleton organization(4). It is involved in converting harmful superoxide radical to oxygen and hydrogen peroxide which is then further broken down by catalase.





AN ADDITIONAL LOOK...

Step-wise regression to further evaluate covariates for model and a 6 covariate analysis with ADG, MMWT, CG, DOB, WW, and sire with the removal of heifers was the best model (highest r^2 and lowest SSE). All covariates had $p < 0.0001$ with the exception of sire $p = 0.21$.

Genome-wide association analysis

- Differences with heifers



AN ADDITIONAL LOOK...

Added


$$DMI = b_0 + b_1(ADG) + b_2(MMWT) + b_3(CG) + b_4(Sire) + b_5(DOB) + b_6(WW) + Animal + e$$

WW=weaning weight

Removed

$$DMI = b_0 + b_1(ADG) + b_2(MMWT) + b_3(CG) + b_4(S) + b_5(DOB) + b_6(DOF) + Animal + e$$


- Removed heifers from analysis



RESULTS


Gene Ontology:

- Blood microparticle(3), NES = 3.2
 - 32 genes with 13 leading edge genes
 - *ACTA1* in common with cytoskeleton organization(4)
- Axon part(4), NES = 2.976
 - 17 genes with 7 leading edge genes





OTHER BREEDS

- Angus



- Simmental Angus



CONCLUSION

- Feed costs are a major expense in cattle production
- Limited records on feed efficiency of cattle have been collected
- Selection for feed efficient cattle will be based on genetic markers that have major effects either individually or collectively as part of a biological pathway



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