Gene Set Enrichment Analysis for Feed Efficiency in Beef Cattle

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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

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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)
WHY A GENOMICS APPROACH?

- Feed intake phenotypes are expensive to measure so the use 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

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RESIDUAL FEED INTAKE (RFI)

- RFI is a measure of feed efficiency that quantifies the variance in feed intake unrelated to level of production (BIF 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

HEREFORD CATTLE

- 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

Animals & Phenotypes

GrowSafe Feeding system at Olsen Ranches

http://www.olsenranches.com/feedtrials.html
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 weight (MMWT), CG, S, DOB and DOF to estimate RFI
  \[
  DMI = b_0 + b_1(ADG) + b_2(MMWT) + b_3(CG) + b_4(S) + b_5(DOB) + b_6(DOF) + \text{Animal} + \epsilon
  \]

GENETICS

- 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

GENOTYPES

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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

- 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)
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)

- 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)

- 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.

  - 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.

Genome-wide association analysis

- Differences with heifers

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 $p=0.21$.
AN ADDITIONAL LOOK....

Added

\[ DMI = b_0 + b_1(ADG) + b_2(MMWFT) + b_3(CG) + b_4(Sire) + b_5(DOB) + b_6(WW) + \text{Animal} + e \]

\[ WW = \text{weaning weight} \]

Removed

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• Removed heifers from analysis

RESULTS

Gene Ontology:

• Blood microparticle\( (3)\), NES = 3.2
  - 32 genes with 13 leading edge genes
  - \textit{ACTA1} in common with cytoskeleton organization\( (4)\)

• Axon part\( (4)\), NES = 2.976
  - 17 genes with 7 leading edge genes

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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

This project was supported by National Research Initiative competitive Grant No. 2011-68004-30214 from the USDA National Institute of Food and Agriculture