Supplementary Materials

Review: Biological determinants of between-animal variation in feed efficiency of growing beef cattle

G. Cantalapiedra-Hijar1, M. Abo-Ismail2, G. Carstens3, L. L. Guan2, R. Hegarty4, D. A. Kenny5, M. McGee5, G. Plastow2, A. Relling6, I. Ortigues-Marty1

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**Supplementary Table S1.** Associations between feed efficiency and rumen microbiome in ruminants

|  |  |  |  |  |
| --- | --- | --- | --- | --- |
| *Study#* | *Authors\** | *Animal* | *Method* | *Finding* |
| 1 | Guan et al., 2008 | Beef cattle | PCR-DGGE | Steers with similar RFI host similar bacterial profiles |
| 2 | Zhou et al., 2009 | Beef cattle | Amplicon (clone libraries) | Low-RFI steers host more abundant *Methanobrevibacter* sp. strain AbM4 and *Methanosphaera stadtmanae* but similar total methonogens |
| 3 | Zhou et al., 2010 | Beef cattle | PCR-DGGE | Steers with similar RFI host similar archaeal profiles when fed both growing and finishing diets. *Methanobrevibacter ruminantum strain NT7* was less represented in low-RFI animals |
| 4 | Hernandez-Sanabria et al., 2010 | Beef cattle | PCR-DGGE | 13 phylotypes associated with FCR (including *Prevotella oulorum* and *Succinovibrio sp*); 8 phylotypes associated with RFI |
| 5 | Hernandez-Sanabria et al., 2012 | Beef cattle | PCR-DGGE  and qPCR | *Succinovibrio dextrinosolvens, Robisoniella sp*, *Eubacterium sp* are associated to RFI groups |
| 6 | Carberry et al., 2012 | Beef heifers | PCR-DGGE | *Prevotella* was lower in Low-RFI animals |
| 7 | McCann et al. 2014 | Brahman bulls | Amplicon (454 sequencing) | *Prevotella* was lower in Low-RFI animals. |
| 8 | Jami et al., 2014 | Beef cattle | Amplicon (454 sequencing) | An undefined genus of order RF39 was positive correlated with host RFI. Positive correlations between FCR and Bacteriodales, *Prevotellaceae*, and *Prevotella*, and negative correlations of FCR with family XIII of the *Clostridiales* and several genera of Firmicutes were also reported. |
| 9 | Jewell et al., 2015 | Dairy cows | Amplicon (454 sequencing) | Low-RFI cows host higher abundance of *Coprococcus* and lower abundance of *Anaerovibrio* and *Butyrivibrio*. |
| 10 | Myer et al., 2015 | Beef cattle | Amplicon (Illumina Miseq) | Higher *Dialister*, *Lactobacillus*, *Acidaminococcus*, *Lachnospiraceae* and *Veillonellaceae* in high ADG animals |
| 11 | Shabat et al., 2016 | Dairy cows | Metagenomics (Illumina Hiseq) | Three bacterial species were more abundant in Low-RFI cows (including *Megasphaera elsdenii and Coprococcus cactus*) while seven were less abundant |
| 12 | Ellison et al., 2017 | Lamb | Metagenomics (Illumina HiSeq) | Three bacterial phylotypes (including *Methanobrevibacter smithii)* were more abundant in Low-RFI animals while 8 bacterial phylotypes were less abundant |
| 13 | Perea et al., 2017 | Lamb | Amplicon (Illumina Miseq) | Three bacterial phylotypes were more abundant Low-RFI animals while 3 bacterial phylotypes were less abundant (including *Succinivibrio spp.*) |
| 14 | Li et al., 2016 | Beef cattle | Metatranscriptomics | *Methanomassiliicoccales* tended to be more abundant in Low-RFI animals while *Lachnospiraceae*, *Lactobacillaceae*, *Veillonellaceae* tended to be less abundant; |
| 15 | Zhou et al., unpublished data | Beef cattle | Amplicon (454 sequencing) | Nineteen differential abundant phylotypes in rumen content samples and 19 differential abundant phylotypes in rumen tissue samples were found to be associated with host feed efficiency. |

\* References are listed at the end of the Supplementary materials

ADG: average daily gain, FCR: feed conversion ratio, PCR-DGGE: polymerase chain reaction and denaturing gradient gel electrophoresis**,**

RFI: residual feed intake

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| --- | --- | --- | --- | --- | --- |
| *Study#* | *Authors\** | *Animal* | *Intake rate* | *Growth rate* | *Finding* |
| *Higher feed efficiency is associated with lower protein turnover rates* | | | | | |
| 16a | Tomas et al., 1991 | Poultry | Decreases | Increases | Lower muscle FPDR in lines selected for feed conversion efficiency |
| 17 | Mc Carthy et al., 1994 | Fish | Similar3 | Increases3 | Lower WB6-FPDR in individuals with higher growth efficiency |
| 18 | Houlihan et al., 1995 | Fish | Similar3 | Increases3 | Lower WB6-FPDR in individuals with higher protein retention efficiency |
| 19 | Oddy et al., 19951 | Lamb | Decreased | Unknown | Lower muscle FPDR at high intakes in lines selected for growth |
| 20 | Carter et al., 1998 | Fish | Decreases | Increases | Lower WB6-FPDRs in individuals with higher protein growth efficiency |
| 21 | Oddy et al., 19981 | Cattle | Similar4 | Increases | Lower muscle FPDR at high intakes in lines selected for growth |
| 22 | McDonagh et al., 2001 | Cattle | Decreases5 | Similar5 | Higher calpastatin activity in muscle of high feed efficiency individuals |
| 23 | Dobly et al., 2004 | Fish | Similar | Increases | Lower WB6-FPDR in individuals with higher protein growth efficiency |
| 24 | Smith et al., 2011 | Pig | Decreases5 | Similar5 | Higher calpastatin activity in muscle of high feed efficiency |
| 25 | Cruzen et al., 2013 | Pig | Decreases5 | Similar5 | Higher calpastatin activity in muscle of high feed efficiency individuals |
| *Higher feed efficiency is associated with no changes in protein turnover rates* | | | | | |
| 16b | Tomas et al., 1991 | Poultry | Increases | Increases | Similar muscle FPDR in lines selected for growth efficiency |
| 26 | Carter et al., 1993 | Fish | Similar3 | Increases3 | Similar WB6-FPDR in high vs low protein growth efficiency groups |
| 27a | Richardson et al., 2004 | Cattle | Decreases5 | Similar5 | Similar FPDR in muscle of high feed efficiency group |
| 28 | Gomes et al., 2012 | Cattle | Decreases5 | Similar5 | Similar calpastatin activity in muscle of high feed efficiency line |
| 29 | Gomes et al., 2013 | Cattle | Decreases5 | Similar5 | Similar muscle FPDR in high feed efficiency line |
| 30 | Castro-Bulle et al., 2014 | Cattle | Decreases5 | Similar5 | Similar muscle FPDR in high feed efficiency line |
| *Higher feed efficiency is associated with higher protein turnover rates* | | | | | |
| 31 | Martinez et al., 2000 | Fish | Decreases | Increases | Calculated WB6-FPDR was 4 folds higher in transgenic high efficiency line |
| 32 | Pym et al., 2004 | Poultry | Decreases | Decreases | Higher muscle FPDR in selected lines with associated higher feed efficiency |
| 27b | Richardson et al., 2004 | Cattle | No reported | No reported | Positive correlation between feed conversion efficiency and muscle FPDR |

**Supplementary Table S2.** Association between feed efficiency and protein turnover (fractional protein degradation rate; FPDR) in growing livestock species reported in the literature

\* References are listed at the end of the Supplementary materials

1 The experiments of Oddy et al. (1995, 1998) did not measure directly feed efficiency, but high the growth line was previously shown to have lower FCR

3 Comparisons are made by choosing individuals with similar intake but different growth rates (close to the concept of residual gain)

4 Intake was restricted at 1.6 x Maintenance

5 Individuals are classed according to residual feed intake (RFI)

6 Whole-body

**Supplementary Table S3**. Associations between feed efficiency and hormones concentration in growing cattle reported in the literature.

|  |  |  |  |
| --- | --- | --- | --- |
| *Study#* | *Authors\** | *Diet/Treatment†* | *Finding* |
| *Association between IGF-1 concentration and feed efficiency* | | | |
| 28 | Johnston et al., 2002 | High-forage diet | Negative association with RFI |
| 29 | Moore et al., 2005 | High-forage diet | Negative association with RFI |
| 30 | Brown, 2005 | High-forage diet | Negative association with RFI and FCR at d 0, but not on d 70-77 |
| 31 | Wolcott et al., 2006 | High-concentrate diet | Positive association between post-weaning IGF-1 and RFI |
| 32a | Johnston, 2007 | High-forage diet | Negative association with RFI |
| 32b | Johnston, 2007 | High-concentrate diet | Positive correlation with RFI |
| 33a | Lancaster et al., 2008 | Forage-diet | Trend for a negative association with RFI |
| 33b | Lancaster et al., 2008 | High-grain diet | No association with RFI |
| 34 | Kelly et al., 2010 | 70:30 C/F diet | Negative association with RFI on the d 82 but not on d 1, 30 and 60 |
| 35 | Dudi and Datt, 2015 | 40% concentrate diet | Positive association with RFI |
| *Association between Leptin concentration and feed efficiency* | | | |
| 36a | Richardson et al., 2004 | Starter and growing diet | No association with RFI or FCR |
| 36b | Richardson et al., 2004 | Finishing diet | Positive association with RFI but not with FCR |
| 30 | Brown, 2005 | High-forage diet | No association with RFI or FCR at the beginning or end (d 70 -77) of the study |
| 37 | Nkrumah et al., 2007 | High concentrate diet | Positive association with RFI |
| 34 | Kelly et al., 2010 | 70:30 C/F diet | Positive association with FCR but not with RFI |
| 35 | Kelly et al., 2010 | High-concentrate diet | Positive association with FCR but not with RFI |
| 38 | Walker et al., 2015 | High-forage diet | No association with RFI |
| 39 | Foote et al., 2016 | High-concentrate diet | Positive association with RFI at d 83, but not at d 42 and d 83  Negative association with FCR at d0 but not at d 42 and d 83 |
| *Association between Cortisol concentration and feed efficiency* | | | |
| 36c | Richardson et al., 2004 | Group pen | No association with RFI |
| 36d | Richardson et al., 2004 | Metabolic Pen | Positive association with RFI |
| 40a | Montanholi et al., 2009 | Group pen | Positive association with RFI and negative association with FCR |
| 40b | Montanholi et al., 2009 | Group pen, groups divided by RFI | No association with RFI |
| 41a | Montanholi et al., 2013 | Group pens, analysed over days | No association with RFI |
| 41b | Montanholi et al., 2013 | Group pens, analysed over hours | No association from 1 AM to 5 PM, positive association from 6 PM to 12 AM |
| 42 | Nascimento et al., 2015 | Individual feed cattle | No association with RFI |
| 43 | Foote et al., 2016 | Group pen | Positive association with RFI and negative association with FCR |

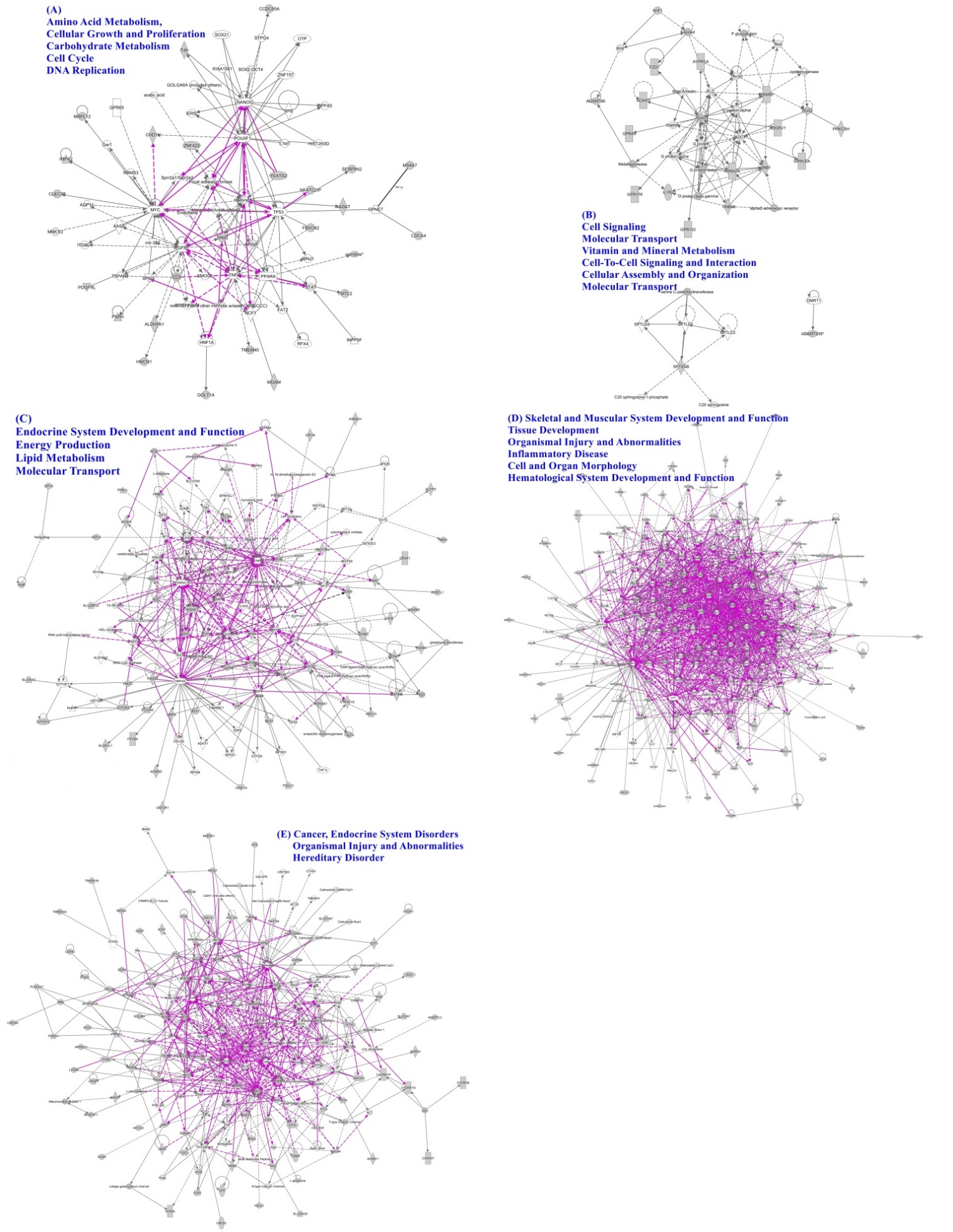
\* References are listed at the end of the Supplementary materials

†Diets are described for IGF-1 and leptin whereas type of treatment only refers to Cortisol.

FCR: feed conversion ratio, RFI:residual feed intake, C/F: concentrate to forage ratio



**Supplementary Figure S1.** Relationships between metabolisable energy intake and retained energy in low and high Residual Feed Intake steers, calculated from published results.

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**Supplementary Figure S2**. Gene interaction network for genes, protein, metabolites associated with feed efficiency in beef cattle reconstructed using Ingenuity Pathway Analysis (Ingenuity Systems,[www.ingenuity.com/](http://www.ingenuity.com/)).

## **Supplementary Material SM1. Candidate genes and Genome-Wide Association Study underlying animal-to-animal variation in feed efficiency in beef cattle**

Genes involved in physiological processes related to traits of interest (e.g. feed efficiency) are called “candidate genes”. Variation in these genes may cause a significant change in gene expression or protein function to explain differences among animals ([Abo-Ismail et al., 2013](#_ENREF_1)). For example, [Karisa et al. (2013](#_ENREF_11)) identified 24 genes associated with RFI and accounted for 19.7% of the phenotypic variation. Analysis of the gene networks suggested three hubs. The first, associated with the Ubiquitin C (*UBC*) gene and interactions with 10 other genes, including Calpastatin (CAST), Insulin-induced gene 1 (INSIG1) and growth hormone receptor precursor (GHR). These genes affect feed efficiency through post-translational regulation processes such as protein degradation, DNA repair, cell cycle regulation, kinase modification, and endocytosis ([Karisa et al., 2013](#_ENREF_11)). For instance, the *UBC* gene is involved in major pathways for protein degradation including ubiquitin-dependent degradation by the proteasome and lysomes, confirming protein turnover as a potential determinant of animal-to-animal variation in feed efficiency. The second hub was associated with the *INSIG1* gene which interacts with 6 genes involved in energy, lipid and steroid metabolism. The third hub was associated with cell growth, cytokine mediated signalling, immune response and transcription for genes including leptin and growth hormone. Interestingly, the third identified network involved one of the Mitogen-activated protein kinase (MAPK) gene family, the extracellular signal-regulated protein kinase1/2 (*ERK1/2*), which interacts with 5 genes, including GHR. Other studies of RFI identified other genes involved in the MAPK signalling pathway (Chen et al., 2011; Rolf et al., 2012; [Abo-Ismail et al., 2014](#_ENREF_2)). The MAPKs are involved in signal transduction pathways for different cellular processes, such as cell division, differentiation, and cell death as a response to hormone and stress. Polymorphism within the tyrosinase (*TYR*) gene which is involved in tyrosine and riboflavin (vitamin B2) metabolism, and catecholamine biosynthesis was associated with changes in FCR ([Abo-Ismail et al., 2014](#_ENREF_2)). In this sense, one of the most interesting positional candidate gene of RFI revealed by the genome wide association study (GWAS) by Seabury et al. (2017) produced the only known enzymatic source of Vitamin B2. Vitamin B2 plays a crucial role as a cofactor of numerous enzymes in cellular oxidative metabolism and a recent study suggested vitamin B2 as a putative biomarker for FCR ([Meale et al., 2017](#_ENREF_14)). These results support the proposal that tissue metabolism and stress as well as protein turnover account for a high proportion of the variation in RFI ([Richardson and Herd, 2004](#_ENREF_18)).

Genes such as Neuropeptide Y, Insulin-like growth factor 2 (*IGF2*), Ghrelin and, Uncoupling protein 2, were also reported to affect feed efficiency ([Sherman et al., 2008](#_ENREF_23)), through their roles in appetite and growth regulation, energy expenditure, efficiency of mitochondrial ATP production, insulin regulation and basal metabolic rate determination. These findings are in agreement with the observation of different heat production (Basarab et al 2003) and mitochondrial function (Bottje and Carstens, 2009) between low and high RFI lines.

As feed efficiency and its component traits are controlled by many genes, detection of a large number of variants in these genes is necessary in order to accurately predict or identify efficient animals. Thus, the use of markers associated with these candidate genes remains limited. Nevertheless, some of these genes or markers have been used in breeding programs to improve feed efficiency including IGF-I, CAST and leptin.

In the last 10 years GWAS have emerged to overcome limitations of the candidate gene approach. [Rolf et al. (2012](#_ENREF_19)) identified 66 SNPs that accounted for 30% of RFI genetic variance, including 17 SNPs previously reported, and involved genes impacting cell growth and death, metabolic disorders, amino acid and lipid metabolism and signal transduction including calcium and MAPK signalling pathways.

Other GWAS results suggested genes impacting lipid and energy metabolism as markers of RFI ([Saatchi et al., 2014a](#_ENREF_20); [Seabury et al., 2017](#_ENREF_22)). [Seabury et al. (2017](#_ENREF_22)) reported several genes related to RFI (including member RAS oncogene family (*RAB28*) and discs large MAGUK scaffold protein 1 (*DLG1*)) linked to adipogenesis, obesity, diabetes, glucose uptake and mitochondrial function. Saatchi et al. (2014) highlighted two genes related to RFI involved in efficiency of ATP use during mechanical force (DNAH17) and cellular calcium/phosphate homeostasis and muscle growth inhibition (STC2). Interestingly, none of these two genes were related to DM intake or growth rate, suggesting their potential role as true determinants of growth efficiency.

The candidate gene and GWAS results suggested that MAPK and calcium signaling pathway, cellular energy transduction and fatty acid degradation (β-oxidation) and growth hormone as the most important biological mechanisms contributing to variation in feed efficiency.

## **Supplementary Material SM2. Gene Expression and Transcriptomics underlying animal-to-animal variation in feed efficiency in beef cattle**

Transcription profiling has provided several new insights into the molecular basis of efficiency. In a global gene expression analysis using microarrays of RNA from high and low RFI animals, one hundred and sixty-one unique genes were identified ([Chen et al., 2011](#_ENREF_6)). These genes are involved in several gene networks affecting cellular growth and proliferation (25 genes), cellular assembly and organization (17 genes), protein synthesis (13 genes), endocrine system development and lipid metabolism (13 genes), carbohydrate metabolism (13 genes) and cell death and signaling (12 genes). The majority of up-regulated genes in low RFI animals were stimulated by MAPKs ([Chen et al., 2011](#_ENREF_6)), emphasizing the importance of this pathway and confirming the results discussed above. A more recent study used RNA sequencing (RNAseq) to evaluate the liver transcriptome ([Alexandre et al., 2015](#_ENREF_3)). Inflammation, immune response, migration and proliferation of T cells, response to stress (all increased in inefficient animals) and lipid and energy metabolism were identified as the most important biological mechanisms. After validating their results by performing serum biochemistry and liver histopathology, they suggested that the stress caused by the altered lipid metabolism and/or the increase of bacterial infection due to higher feed intake as the inefficient animals showed hepatic periportal lesions. In contrast, another RNAseq study ([Weber et al., 2016](#_ENREF_24)) showed an increase in immune system and inflammatory response in the duodenum and other tissues together with a reduction in fat deposition in the progeny of an efficient sire compared with progeny of an inefficient sire. Difference associations between inflammation and immune response and efficiency may be due to the diet composition or sensitivity (e.g. high grain diet or roughage) or be population specific. In a different study, efficient heifers had high expression of genes in the liver that were modulated by interferon signaling, pointing towards better innate immunity allowing greater use of intake energy toward growth and production ([Paradis et al., 2015](#_ENREF_16)).

In addition, in the study by [Weber et al. (2016](#_ENREF_24)) 633 differentially expressed genes were noted between the progeny groups across tissues where most of these genes were linked to i) immune and inflammatory response, ii) the reduction of fat deposition in the adipose tissue and iii) an increase in muscle growth, supporting the observed high lean:fat ratio in the carcass characteristic of progeny of the efficient sire.

Other gene expression analyses confirmed the importance of mitochondrial respiration, the actin cytoskeleton and signaling pathways suggested by GWAS and candidate genes. In liver, *UCP2* and transcription factor A mitochondrial (*TFAM*) genes were highly expressed in liver tissue from efficient Nellore cattle compared to those selected as inefficient, whereas in muscle tissue *TFAM* showed higherexpression for the inefficient animals than the efficient group ([Fonseca et al., 2015](#_ENREF_8)). The *UCP2* product mediates mitochondrial proton leakage and TFAM is a major regulator of mitochondrial biogenesis ([Fonseca et al., 2015](#_ENREF_8)). Using RNAseq, [Kong et al. (2016](#_ENREF_13)) reported that genes involved in remodeling of epithelial adherent junctions were up-regulated in efficient animals and suggested higher cell mobility and dynamic remodeling as well as an increase of cell turnover within the gut epithelium of efficient animals. Genes involved in actin cytoskeleton and signaling pathways were up-regulated in the rumen epithelial of efficient animals which would potentially result in greater absorption of nutrients ([Kong et al., 2016](#_ENREF_13)).

## **Supplementary Material SM3. Proteomic and Metabolomic Analyses underlying animal-to-animal variation in feed efficiency in beef cattle**

Only a few studies of feed efficiency in beef cattle have been performed using proteomic approaches. Nevertheless, they have yielded interesting results. For example,14-3-3 protein epsilon, and Actin, alpha 1, skeletal muscle proteins were highly abundant in inefficient animals compared with efficient individuals ([Carvalho, 2016](#_ENREF_4)). In the same study, Heat shock protein beta 1 was more abundant in efficient animals than inefficient animals. These three proteins are involved in protein degradation and turnover and support this mechanism as an important determinant of animal-to-animal variation in feed efficiency. In addition, in liver tissue, 10-Formyltetrahydrofolate dehydrogenase (ALDH1L1) was more abundant in efficient animals compared with inefficient animals. The *ALDH1L1* gene encodes an enzyme which is involved in metabolism of water-soluble vitamins (B9) and cofactors (Pterin). ALDH1L1 can reduce the negative effect of reactive oxygen species by working as an antioxidant for the oxidative stress due to accumulation of ROS and sparing cell energy for growth. As the correlation between gene expression using mRNA and protein levels is moderate due to posttranscriptional modifications or regulation, the need for further studies using proteomic tools is required for identifying putative protein biomarkers for feed efficiency in beef cattle.

Analysis of individual metabolites or the whole metabolome has been used to identify potential biomarkers to evaluate feed efficiency ([Clemmons et al., 2017](#_ENREF_7); [Karisa et al., 2014a](#_ENREF_10); [Meale et al., 2017](#_ENREF_14)). For example, 14 plasma metabolites were associated with RFI in feedlot steers ([Karisa et al., 2014a](#_ENREF_10)). Some of these metabolites such as creatine and citrate indirectly affect the cholesterol metabolism via the influence on the level of one of the key kinases, AMP-activated protein kinase (AMPK), previously identified by genomics data (see above), resulting in an impact on the efficiency of the glucose transporter and cholesterol metabolism. In addition, inefficient steers had high cholesterol levels compared with efficient steers. This positive correlation was proposed to be due to the fact that the pattern of regulation of cholesterol biosynthesis is similar to the regulation of lipid metabolism in the cell which matches the positive correlation between RFI and fattening. In a recent study, lower plasma concentrations of Glycine, as well as its intermediate Sarcosine, was observed in efficient bulls ([Meale et al., 2017](#_ENREF_14)) agreeing with the study by Karisa et al (2014a). Using LC-MS untargeted metabolomics, homocysteine, pantothenate (i.e. vitamin B5), carnitine and glutamine showed lower concentrations in the serum of inefficient steers compared with efficient ones ([Clemmons et al., 2017](#_ENREF_7)). These metabolites play a key role in amino acid, carbohydrate, and fat metabolism as well as protein synthesis. [Weikard et al. (2010](#_ENREF_25)) provided evidence that mutation in the non-SMC condensin I complex, subunit G (NCAPG) had an effect on arginine metabolism supporting the link between NCAPG and efficiency of growth. They also reported a mutation in the growth differentiation factor 8 (GDF8) gene (myostatin), that raised the carnitine level and glycerophosphatidylcholines and sphingomyelins supporting the role of as a potential modulator of growth in cattle. Another metabolite, β-hydroxybutyrate, a product of lipolysis, was also reported to be a biological indicator of feed efficiency in beef cattle where it is positively correlated with RFI ([Karisa et al., 2014a](#_ENREF_10)). In a second study [Karisa et al. (2014b](#_ENREF_12)), reported creatine, hipurate and carnitine were validated and explained 32% of the phenotypic variation in RFI. The authors proposed these metabolites as a potential selection tool. A metabolite such as carnitine that is validated in more than two studies can be a potential biomarker for identifying efficient individuals within beef cattle herds. Metabolite biomarkers (or “metabotype”) can be potential predictors or indicators of feed efficiency and can be incorporated in genetic improvement programs in beef cattle.

## **Supplementary Table S4.** Genes, protein, metabolites and biological functions underlying animal-to-animal variation in feed efficiency in beef cattle

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| --- | --- | --- | --- | --- | --- |
|  | |  | Molecular finding | |  |
| Approach and Study | Genes, protein and metabolites associated to feed efficiency | | | Associated biological  function | |
|
| *Candidate Genes and*  *Genome-Wide Association Study* |  | | |  | |
|  |  | | |  | |
| Study#44 (Karisa et al., 2013) | First hub: Ubiquitin C gene (UBC) interacting with PLEKHA7, PARP14, SMARCAL1, UBA5, LRP5, **CAST**, **GHR**, OSMR, or LIFR. | | | Endoplasmic reticulum associated **degradation of proteins** (ERAD), lysosomal degradation, **protein degradation** via the proteasome, activation of transcription factor NF-κB, cell signaling, and DNA repair | |
| Second hub: Insulin-induced gene 1 (INSIG1) interacting with LPCAT3, ACSS2, AACS, ERLIN2, HMGCS2 | | | **Energy, lipid** and steroid **metabolism** | |
| Third hub: Leukemia inhibitory factor receptor interacting with GP130, CLCF1, **ERK1/2 (MAPK)**, STAT5, **GHR**, and OSMR | | | Growth, cytokine mediated signalling, and **immune responses.** ERK1 is a protein kinase involved in **cell growth**, adhesion, survival, and differentiation by regulating transcription, translation, cytoskeleton rearrangements and lysosome processing and endosome cycling | |
| Study#45 (Abo-Ismail et al., 2013) | PRSS2 and CCKBR | | | **Digestion, proteolysis**  **Regulation of intake** and pancreatic secretions | |
|  |  | | |  | |
| Study#46  (Abo-Ismail et al., 2014) | ELP3, HMCN1, ZNF423, PPM1K, RASA1, CACNA1G and STK3 (**MAPK**) and **TYR** | | | **Ion and cation transport**  **Proteolysis**, protein complex biogenesis, protein amino acid glycosylation. **MAPK:** Signal transduction pathways to activate different cellular processes such as cell division, **cell differentiation and cell death** as a **response to stress** and hormones. **Riboflavin metabolism**, melanogenesis, Tyr metabolism and catecholamine biosynthesis | |
| Study#47 (Sherman et al., 2008) | NPY, IGF2, GHRL, **GHR** and **UCP3** | | | Central **appetite stimulator**, feed intake regulation, **growth regulation**, **energy partitioning and expenditure**, insulin regulation, basal metabolic rate regulation and efficiency of ATP production | |
| Study#48 (Rolf et al., 2012) | 66 SNPs (17 previously reported) | | | **Cell growth and death**, metabolic disorders, **amino acid and lipid metabolism**, **immune and endocrine systems**, and signalling transduction including the **MAPK** and calcium signalling pathways | |
| Study#49 (Saatchi et al., 2014) | 10 SNPs  **DNAH17**, STC2 and C16orf72 | | | Dyneins proteins use ATP to generate mechanical force in processes such as **cellular division, intracellular transport** **and mitosis.** Bone and skeletal **muscle growth**  Renal and intestinal calcium and phosphate transport, **cell metabolism**, or cellular calcium/phosphate homeostasis | |
| Study#50 (Seabury et al., 2017) | ANGUS: XIRP2, HSPB8, DDB1, **DAK**, APDRHL1, CDC-16 (most previously associated with feed efficiency and growth) | | | **Growth** efficiency, human **obesity** and **energy production**. **Riboflavin metabolism: metabolism of carbohydrates, amino acids and fatty acids** | |
| HEREFORD: **DNAH17**,RAB28, DLG1, PTPN22, RBSBN1 | | | Human **obesity**, **Adipogenic differentiation**, Type 1 **diabetes** and glucose uptake | |
| SIMMENTAL X ANGUS: STX3, MRPL16, GIF, TCN1, LOC101906936, LUZP2, OR9Q2, TMEM72, **TMEM40** (previously reported in dairy cows) UCN3, CST7 | | | **Obesity**, **growth, diabetes, mitochondrial function, Vit B**12 binding proteins, Olfactory receptors | |
| *Gene expression and Transcriptomics* |  | | |  | |
|  |  | | |  | |
| Study#51 (Chen et al., 2011) | 161 genes in liver  7 gene networks:   1. Most genes are upregulated through interaction with PDGF. This network includes **GHR** and **IGFBP3** 2. Most of the up-regulated genes are activated by MAPKs pathway. Down-regulated genes included AHR, CYP1A2, GSTM1 and GSTT1 3. Including IDH2 and GBAS. 4. Genes that interact with two transcription factors: TP53 and MYC. Upregulated genes include COL14A1, FMOD, WRN, MRPL12, IMPA2 and MSH5. The downregulated genes include ARPCB1, CPEB1, SERPINI2, IGHG1 and RSP27 5. Includes IVD, **CYP2**C18 and SLC27A6 6. ABCC4 and ABHD5 7. Network 7 is important in cell signalling through TNF and include **SOD3 and IRX3** genes | | | **Cellular growth and proliferation,** cancer, cardiovascular system development and function  **Cellular growth and proliferation, hepatic system disease**. Expression of several detoxification enzymes, particularly the cytochrome P450s and involved in **oxidation stress**  Cellular assembly and organization, cancer, and movement as well as mitochondrial function  **Protein synthesis,** development disorder, neurological disease  Drug and **lipid metabolism and Endocrine system development**  Drug and **carbohydrate metabolism** and triacylglycerol homeostasis.  **Cell proliferation death, cell signalling, molecular transport** | |
| Study#52 (Alexandre et al., 2015) | 8 genes (including **CYP2**E1, FASN, **SOD3**, RHOB, GADD45 and NR0B2 | | | **Liver inflammatory response , lipid metabolism, immune response**, and **response to** **stress** | |
| Study#53 (Weber et al., 2016) | 633 differential expressed genes in different tissues, including some previously linked to feed efficiency (**IRX3**, **LHX3**, MYOD1, ETS1) and other important genes (SIX3, PCSK2, HHEX, CDKNA2A/B, GATA3, STAT3, **MYT1**, E2F1, ZEB1) | | | **Immune and inflammatory response**, **lipid metabolism,** and **muscle growth** | |
| Study#54 (Kelly et al., 2011) | COX II, **UCP3**, PGC-1α, PPAR-γ | | | **Cellular (mitochondrial) energetic efficiency** | |
| Study#55 (Fonseca et al., 2015) | TFAM, UCP2 in liver  TFAM in muscle | | | **Mitochondrial biogenesis and transcription**  **Mitochondrial proton leakage (prevent formation of ROS)**  **ATP production**  **Immune function** | |
| Study#56 (Kong et al., 2016) | 122 genes in rumen epithelium including  p120ctn, v-Src, IQGAP1, DNM2, HGS, ACTB, TUBB, TUBA4A, EIF2, Rho family GTPases, Ephrin B signaling | | | Remodelling intercellular adhesion through adherens junctions  **Protein and cell turnover**  Cytoskeletal organization | |
| *Proteomic and metabolomic* |  | | |  | |
|  |  | | |  | |
| Study#57 (Carvalho, 2016) | YWHAE, ACTA1, HSP27, 14-3-3 epsilon ALDH1L1 | | | **Degradation of proteins**  **Differentiation, cellular development, response to stress and signal transduction**  Reducing the rate of apoptosis  Metabolism of water-soluble **vitamins (B**9) and cofactors (Pterin) | |
| Study#58  (Karisa et al., 20104) | Creatine, **Glycine,** Threonine, **Carnitine**, acetate, Creatine, phenylalanine, lysine, Citrate, Betaine, Glutamate, Hippurate, hydroxyisobutyrate, Tyrosine and formate | | | AMPK signaling, **Glutathion** metabolism and Lysine degradation  **MAPK pathway,** Amino acid metabolism, urea cycle and GABA receptor signaling  Metabolism of nitrogen, pyruvate, methane  Protein kinase signalling and dopamine receptor signaling | |
| Study#59  (Clemmons et al., 2017) | Pantothenate (**Vitamin B**5), **Homocysteine**, Glutamine, **Carnitine** | | | **Metabolism of carbohydrate, amino acid and fat**  Cysteine-**Methionine metabolism**, **protein synthesis**  **Muscle growth and** decreased muscle catabolism  Fatty acid transport to the mitochondria for **β-oxidation** | |
| Study#60 (Meale et al., 2018) | **Vitamin B2**, carnosine, **Glycine**, Sarcosine, Propionyl**carnitine**, Aspartate, Serine | | | Oxidative metabolism (cycle krebs) and **β-oxidation** of fatty acids. Amino acid catabolism, Choline-**Methionine metabolism.** Gluconeogenesis | |

## Bold character genes, proteins, metabolites and biological functions which were found in other studies.

References are listed at the end of the Supplementary materials.

**Supplementary Table S5.** Ingenuity gen network linked to feed efficiency traits in ruminants

|  |  |  |  |  |
| --- | --- | --- | --- | --- |
| ID | Molecules in Network | Score | Focus Molecules | Top Diseases and Functions |
| 1 | ACTB,Actin,AHSG,Alpha catenin,ARPC1B,CD59,CEP83,CEP295,CFL1,Ck2,Creb,DNM2,EGF, ESPN, F Actin,Fam13a, G-Actin,hemoglobin,LYPD6,MYL12A,NINL,PALLD,Pld,PLEKHA7,PPM1H, PPP1R12A,PTPN13,RAI14,Ras homolog,RHOG,Rock,SH3PXD2A,SIRPA,Spectrin,STK35 | 39 | 24 | Cellular Assembly and Organization, Cellular Function and Maintenance, Cancer |
| 2 | Ap2 alpha,ARRDC3,Cdc2,CPEB1,Cyclin A, Cyclin D,DACH1,DTNA,ENaC,HGS,L-phenylalanine,MAOA,Mitochondrial complex 1,Mlc,MSLN,MTCH2,NDUFAF1,NEDD4,Notch,OCLN, PI3K (complex),PI3K p85,PP1 protein complex group,PP2A,PTN, pyruvate kinase,Rb,REPS2,RPS6KB2,SHC3,SLC25A36,STC2,TFAM, thyroid hormone receptor,UBA5 | 30 | 20 | Cancer, Endocrine System Disorders, Organismal Injury and Abnormalities |
| 3 | ANK3, Atrial Natriuretic Peptide,BIN1,cacn,CACNA1G,CACNA1H,CACNG6,CACNG7,Dynamin, ERK1/2,Fgf,FGF6,FGF23,Fgfr,Ggt,GLDN,glycine,Hspg, L-glutamine,LIFR,N-type Calcium Channel,NELL2,OSMR,PLA2, PLC gamma,SCN9A,SPRY4,Stat5 dimer,STX8,Syntaxin,T-type Calcium Channel,TRIM2,UNC5C,voltage-gated calcium channel, voltage-gated sodium channel | 28 | 19 | Hereditary Disorder, Neurological Disease, Organismal Injury and Abnormalities |
| 4 | 7S NGF,Akt,CNN1,COL14A1,COL2A1,Collagen Alpha1,creatine, creatine kinase,DNA-PK,Fibrin,Fibrinogen,GHR,Glycogen synthase, Growth hormone,Igf,IGF2,Igfbp,IGFBP2,IGFBP3,IGFBP5, L-lysine,L3MBTL3,LRP5,MEP1B,N-Cadherin,PCDH19, PDGF (family),PDGFC,POSTN,RNF150, Secretase gamma,SKAP2,Smad2/3-Smad4,TNC,VitaminD3-VDR-RXR | 28 | 19 | Connective Tissue Development and Function, Skeletal and Muscular System Development and Function, Tissue Development |
| 5 | ABCC4,BDH1,betaine,BEX3, CAR ligand-CAR-Retinoic acid-XRα,CHP1,CRYM,CYP,Cyp1a,CYP1A2,Cyp2b,CYP2B6,CYP2C18, cytochrome-c oxidase,FMOD,glutathione peroxidase, glutathione transferase,GST,GSTM1,GSTM3,Gstt1,JUN/JUNB/JUND, Ldh (complex),NFkB (complex),NKIRAS1,POR,PTPase, PXR ligand-PXR-Retinoic acid-RXRα,RTF1,Rxr,SLC2A5,Sod,SOD3,STAB2,unspecific monooxygenase | 28 | 19 | Drug Metabolism, Endocrine System Development and Function, Energy Production |
| 6 | ACAD11,AHR,Alpha tubulin,ALT,ANGPTL2,APIP,ATF6,Calcineurin protein(s),calpain,CAMK2G,CAPN2,CAPN8,Cbp/p300,citric acid,Cyclin E,DHRS3,E2f,ELP3,estrogen receptor,Hdac,HISTONE,Histone h4,Hsp90,IDH2,IRX3,LDL-cholesterol,N-cor,Nuclear factor 1,P38 MAPK,PDYN,PITX2,SLC22A7,SLC27A6,SOGA1,VIM | 28 | 19 | Cancer, Organismal Injury and Abnormalities, Lipid Metabolism |
| 7 | ABHD5,acetate,ACSL,AMPK,CPT1,GHRL,GPC3,GPC5,HDL,Hedgehog,HHIP,HMG CoA synthase,HSD17B3,INSIG1,Jnk,L-threonine,MYO9A,NADPH oxidase,NOX3,Nr1h,p70 S6k,PEPCK,phosphatase,PPM1L,PRDX4,PRKAA,RNASEL,SLC25A33,SREBF1,Srebp,T3-TR-RXR,transglutaminase,TSH,UCP2,UCP3 | 26 | 18 | Energy Production, Lipid Metabolism, Small Molecule Biochemistry |
| 8 | ACKR3,ADAMTS5,ADCY,ADGRV1,ADRA2A,alpha2-adrenergic receptor,AVPR1A,Beta Arrestin,Clathrin,cyclooxygenase,EDNRB,Frizzled,FZD1,G protein,G protein alpha,G protein alphai,G protein beta gamma,G-protein beta,GNB1,GNB2,Gpcr,GPR45,GPR132,GPR176,GPRC6A,IL1R2,Metalloprotease,Nos,P glycoprotein,Pkc(s),PLC,PRKCSH,RGS2,WIF1,Wnt | 24 | 17 | Cell Signaling, Molecular Transport, Vitamin and Mineral Metabolism |
| 9 | 14-3-3,ADRB,AKT2,Alp,CaMKII,caspase,cytochrome C,FAIM2,GLI2,Gsk3,Ifn gamma,IGF1,Integrin,JINK1/2,L-glutamic acid,L-homocysteine,LANCL1,MAP2K1/2,MKI67,NMDA Receptor,P-TEFb,PARL,PARP,PARP14,PDGF BB,PINK1,PYCR1,RFC5,RPA,RPH3A,SMARCAL1,TCR,TNKS1BP1,Vegf,WRN | 24 | 17 | Cellular Compromise, Neurological Disease, Organismal Injury and Abnormalities |
| 10 | ABCG2,Alpha Actinin,BRF1,CAST,CNGA3,COL1A1,COL3A1,COL4A6, Collagen type I,Collagen type II,Collagen type III,Collagen type IV,Collagen(s),Cpla2,ERK,ETS,ETS2,FGA,GPIIB-IIIA,Laminin1, Laminin (complex),LOXL1,MRPS15,PCSK6, Pdgf (complex),Pkg,S100A10,Smad2/3,TCF, Tgf beta,THBS1,Timp,TIMP1,TIMP3,trypsin | 22 | 16 | Connective Tissue Disorders, Organismal Injury and Abnormalities, Inflammatory Disease |
| 11 | Ap1,C/ebp,CHADL,CNTFR,COL22A1,collagen,DDC,FMO5,HLA-DOB,Hsp27,Ifn,IFN Beta,IL1,IL-1R,IL12 (complex),Immunoglobulin,INHBA,LECT2,LEP,MAP2K6,Mapk,MHC Class II (complex),Ngf,Pde,PDE1A,PDE9A,PHYHIPL,Pka catalytic subunit,Pro-inflammatory Cytokine,Proinsulin,Smad,STEAP4,Tnf (family),Tnf receptor,UGT2B17 | 20 | 15 | Cardiovascular System Development and Function, Cell Morphology, Organ Morphology |
| 12 | ANXA10,APP,Aspartyl Protease,C19orf12,C1orf105,C6orf118,CALML4,CFDP1,Cu+,DNAJC4,FICD,formic acid,GTPase,HTT,IGSF10,KCNIP4,KCNIP4-IT1,KHDRBS3,KIAA0825,LMCD1,MARCH10,MCTP2,Mmp,MYL5,NECAP2,NIM1K,OCIAD2,PDXP,PP2D1,PUSL1,Rbfox3,SMARCA4,TBC1D20,TM4SF19,ZNF706 | 17 | 13 | Cell Morphology, Hematological System Development and Function, Inflammatory Response |
| 13 | AHNAK2,AK3,ANKRD10,APMAP,AR,C16orf72,C9orf64,cortisone,DENND5A,DIP2B,DNAH17,DPP9,ELAVL1,FBXO6,GH1,HEATR1,HOOK3,HSD17B11,IGSF3,IMPA1,INPP4B,IPO11,ISOC1,KDELC2,KIF21A,METTL7A,miR-519a-3p (and other miRNAs w/seed AAGUGCA),MOB3B,NAA25,NAGA,NTRK1,PUS7,RNF214,TBCB,TMX3 | 17 | 13 | Cell Morphology, Developmental Disorder, Hereditary Disorder |
| 14 | ACMSD,ADAT1,ALDH1L1,ALDH8A1,APEH,CDCA5,CES2,DAAM2,DDX60,ETFDH,FAM86C1,FXYD6,GTF2E1,GTF2E2,GTF2F2,HDL-cholesterol,HNF4A,IVD,MFSD1,miR-331-3p (miRNAs w/seed CCCCUGG),NXF1,OBSCN,PHPT1,PQLC2,RNA pol2-transcription factor,RPAIN,SLC45A2,SMYD5,SSR2,SUPT4H1,TAF1L,tretinoin,UGT2A3,UGT3A1,UMPS | 17 | 13 | Drug Metabolism, Lipid Metabolism, Molecular Transport |
| 15 | 26s Proteasome,ATP13A2,CARMIL1,CDH1,Cg,D-pantothenic acid,FSH,GNRH,GOT,HELZ,Hsp70,HSPB1,IgG,IgG1,Igg3,IGHG1,IGLL1/IGLL5,Igm,IL12 (family),Insulin,Interferon alpha,LDL,Lh,MHC,NIPSNAP2,p85 (pik3r),Pka,Rac,RDM1,RFX6,RNA polymerase II,SRC (family),STAT5a/b,TSPAN13,Ubiquitin | 15 | 12 | Developmental Disorder, Hereditary Disorder, Metabolic Disease |
| 16 | AADAT,AASS,acetic acid,ALDH5A1,AQP11,CD3,CLEC3B,Endothelin,Focal adhesion kinase,Gar1,GPR65,Histone h3,HMCN1,IMPA2,INPP5F,ITGBL1,mir-383,MNK1/2,MRPL12,MYC,NFATC2IP,Pdgfr,PDGFRL,PSPH,RBMS3,SERPINB10,SMOC2,SPEG,Sprr2a1/Sprr2a2,STAT,TGFB1,TPM3,TSPAN7,YEATS2,ZNF423 | 15 | 12 | Amino Acid Metabolism, Small Molecule Biochemistry, Drug Metabolism |
| 17 | AC1/8,Akt-Calmodulin-Hsp90-Nos3,AOX1,AVIL,Calm1 (includes others),Calmodulin,Calmodulin-Camk4-Ca2+,Calmodulin-CaMKI-Ca2+,Calmodulin-CaMKII-Ca2+,Calmodulin-Camkk-Ca2+,Calmodulin-Hsp90-Nos3,Calmodulin-Nos3,CNST,CRMP2-KLC1-Tubulin,CTXN1,EVC2,GALNT9,GJA1,GOLIM4,HTR3C,KRAS,LRRTM3,MAP6D1,Ntp,PTPN1,Rnr,RNR3,RPS27,RPS4X,TMEM74,TMEM104,TMEM30A,TUBA4A,TUBB,tubulin | 15 | 12 | Cancer, Gastrointestinal Disease, Organismal Injury and Abnormalities |
| 18 | alcohol group acceptor phosphotransferase,atypical protein kinase C,BCR (complex),CD4,CD3E,CMTM4,Cofilin,DAPK2,Eph Receptor,Ephb,EPHB6,Fcer1,Gm-csf,GRIK1,Ige,JAK,KITLG,L-tyrosine,MAPK1,Mek,MSH5,NCK,Nfat (family),PI3K (family),Raf,Rap1,Ras,Rsk,Sapk,Shc,SORL1,Sos,tubulin (family),tyrosine kinase,VAV | 13 | 11 | Cellular Development, Hematological System Development and Function, Lymphoid Tissue Structure and Development |
| 19 | carnitine,CCDC85A,CDCA4,CHD1L,CPNE7,DPPA5,FAT2,FBXO42,GOLGA6A (includes others),HIST2H3D,Hmgn2 (includes others),IER5L,KIAA1551,L1td1,MGAM,miR-1913 (and other miRNAs w/seed CUGCCCC),MS4A7,NANOG,NCF1,NINJ1,OTP,POU5F1,PPARA,RFX4,RPE,SERPINI2,SOX21,SOX2-OCT4,STPG4,Tdh,TMEM40,TMTC2,TNF,TP53,ZNF157 | 13 | 11 | Cell-To-Cell Signaling and Interaction, Cellular Growth and Proliferation, Connective Tissue Development and Function |
| 20 | 16,16-dimethylprostaglandin E2,ACSL6,acyl-coenzyme A,ACYP2,ASNSD1,BOD1L1,C21orf33/LOC102724023, cerebroside 3-sulfate,COMP,CST5,CYP19, delta-aminolevulinic acid,KRT23,kynurenic acid,lauric acid,LDHA,mir-33,MTORC1,NF2,NT5DC3,OR4X1,PHYH,PLAGL2,PPARGC1A,PPM1K,PTPRA,PTPRM,RRP1,SGPP2,SH3TC2,SLC27A5,SPARCL1,TNF,uridine,VPS25 | 7 | 7 | Lipid Metabolism, Small Molecule Biochemistry, Energy Production |
| 21 | GOLT1A,HNF1A | 2 | 1 | Amino Acid Metabolism, Cancer, Carbohydrate Metabolism |
| 22 | ABHD1,CCDC155 | 2 | 1 | Cell Cycle, DNA Replication, Recombination, and Repair, Cell Morphology |
| 23 | ADAMTS19,DMRT1 | 2 | 1 | Cell-To-Cell Signaling and Interaction, Cellular Assembly and Organization, Cellular Development |
| 24 | C20 sphingosine,C20 sphingosine-1-phosphate,serine C-palmitoyltransferase,SPTLC1,SPTLC2,SPTLC3,SPTSSB | 1 | 1 | Lipid Metabolism, Small Molecule Biochemistry, Molecular Transport |

**Supplementary Table S6.** Biological pathways linked to feed efficiency traits in ruminants using DAVID KEGG pathways analysis

|  |  |  |  |  |
| --- | --- | --- | --- | --- |
| Term | Count | % | P-Value | Genes |
| bta00982:Drug metabolism - cytochrome P450 | 7 | 2.54 | 4.8E-04 | 788719, 517724, 615507, 533587, 503552, 338074, 281293 |
| bta04510:Focal adhesion | 12 | 4.35 | 9.6E-04 | 614055, 281662, 530315, 534923, 280979, 282187, 281530, 613787, 523526, 512696, 327672, 407142 |
| bta04151:PI3K-Akt signaling pathway | 16 | 5.80 | 9.8E-04 | 506083, 540317, 534923, 281885, 281530, 523526, 281201, 281202, 514720, 530315, 530239, 280805, 282187, 613787, 327672, 407142 |
| bta00380:Tryptophan metabolism | 6 | 2.17 | 1.1E-03 | 515030, 503552, 338074, 520638, 280762, 281293 |
| bta05218:Melanoma | 7 | 2.54 | 1.5E-03 | 530315, 540317, 282637, 530239, 534923, 613787, 327672 |
| bta00830:Retinol metabolism | 6 | 2.17 | 3.0E-03 | 281482, 533587, 503552, 535243, 338074, 504769 |
| bta05200:Pathways in cancer | 16 | 5.80 | 3.9E-03 | 497019, 540830, 529131, 445417, 540317, 534923, 281885, 510255, 523526, 281201, 281202, 530315, 530239, 282637, 327672, 281750 |
| bta04015:Rap1 signaling pathway | 11 | 3.99 | 4.0E-03 | 530315, 540317, 282637, 530239, 534923, 281885, 280979, 281530, 613787, 286883, 327672 |
| bta05219:Bladder cancer | 5 | 1.81 | 4.9E-03 | 529131, 530315, 282637, 281530, 327672 |
| bta04010:MAPK signaling pathway | 12 | 4.35 | 5.1E-03 | 521616, 516099, 539969, 530315, 515700, 540317, 530239, 534923, 286883, 327672, 282411, 282412 |
| bta05204:Chemical carcinogenesis | 6 | 2.17 | 7.3E-03 | 517724, 615507, 533587, 503552, 535243, 504769 |
| bta04066:HIF-1 signaling pathway | 7 | 2.54 | 7.4E-03 | 506083, 282092, 530315, 534923, 526999, 282162, 327672 |
| bta04014:Ras signaling pathway | 11 | 3.99 | 7.7E-03 | 530315, 540317, 530239, 534923, 281148, 281885, 613787, 512696, 327672, 281201, 281202 |
| bta05205:Proteoglycans in cancer | 10 | 3.62 | 8.8E-03 | 615239, 506083, 445417, 282094, 534923, 280979, 282162, 281530, 281240, 327672 |
| bta05100:Bacterial invasion of epithelial cells | 6 | 2.17 | 1.1E-02 | 326600, 282637, 280979, 512696, 538559, 511691 |
| bta04974:Protein digestion and absorption | 6 | 2.17 | 1.5E-02 | 540701, 521058, 282187, 523526, 781493, 407142 |
| bta04012:ErbB signaling pathway | 6 | 2.17 | 1.7E-02 | 506083, 530315, 534923, 282162, 512696, 327672 |
| bta00140:Steroid hormone biosynthesis | 5 | 1.81 | 1.7E-02 | 533587, 503552, 535243, 616934, 504769 |
| bta05214:Glioma | 5 | 1.81 | 2.6E-02 | 530315, 534923, 282162, 512696, 327672 |
| bta04713:Circadian entrainment | 6 | 2.17 | 2.7E-02 | 282162, 327672, 282411, 281201, 281202, 282412 |
| bta04810:Regulation of actin cytoskeleton | 9 | 3.26 | 3.2E-02 | 614055, 326600, 530315, 540317, 530239, 280979, 613787, 534553, 327672 |
| bta04726:Serotonergic synapse | 6 | 2.17 | 5.1E-02 | 535243, 327672, 280762, 281201, 281293, 281202 |
| bta04060:Cytokine-cytokine receptor interaction | 9 | 3.26 | 5.5E-02 | 539548, 514720, 280836, 530315, 509585, 515700, 280805, 281885, 539504 |
| bta04350:TGF-beta signaling pathway | 5 | 1.81 | 5.6E-02 | 506721, 281867, 506083, 281530, 327672 |
| bta05213:Endometrial cancer | 4 | 1.45 | 5.9E-02 | 530315, 282637, 534923, 327672 |
| bta04666:Fc gamma R-mediated phagocytosis | 5 | 1.81 | 6.0E-02 | 326600, 506083, 534923, 534553, 327672 |
| bta04145:Phagosome | 7 | 2.54 | 6.2E-02 | 511582, 615087, 280979, 282493, 526999, 281530, 777775 |
| bta04540:Gap junction | 5 | 1.81 | 6.9E-02 | 530315, 615087, 613787, 327672, 777775 |
| bta04611:Platelet activation | 6 | 2.17 | 7.0E-02 | 614055, 534923, 280979, 282187, 327672, 407142 |
| bta04728:Dopaminergic synapse | 6 | 2.17 | 7.2E-02 | 534923, 282162, 280762, 281201, 281293, 281202 |
| bta04320:Dorso-ventral axis formation | 3 | 1.09 | 7.5E-02 | 281148, 514174, 327672 |
| bta04640:Hematopoietic cell lineage | 5 | 1.81 | 7.6E-02 | 505574, 515700, 281885, 281054, 407098 |
| bta00980:Metabolism of xenobiotics by cytochrome P450 | 4 | 1.45 | 8.3E-02 | 517724, 615507, 533587, 503552 |
| bta05231:Choline metabolism in cancer | 5 | 1.81 | 9.4E-02 | 506083, 530315, 534923, 613787, 327672 |
| bta04916:Melanogenesis | 5 | 1.81 | 9.4E-02 | 445417, 281885, 282162, 327672, 281750 |
| bta05216:Thyroid cancer | 3 | 1.09 | 1.0E-01 | 497019, 282637, 327672 |
| bta04261:Adrenergic signaling in cardiomyocytes | 6 | 2.17 | 1.1E-01 | 521616, 497019, 539969, 534923, 282162, 327672 |
| bta05031:Amphetamine addiction | 4 | 1.45 | 1.1E-01 | 281385, 282162, 280762, 281293 |
| bta04630:Jak-STAT signaling pathway | 6 | 2.17 | 1.2E-01 | 539548, 514720, 280836, 534923, 280805, 539504 |
| bta04725:Cholinergic synapse | 5 | 1.81 | 1.2E-01 | 534923, 282162, 327672, 281201, 281202 |
| bta05146:Amoebiasis | 5 | 1.81 | 1.3E-01 | 516099, 515700, 282187, 523526, 407142 |
| bta00750:Vitamin B6 metabolism | 2 | 0.72 | 1.3E-01 | 506308, 338074 |
| bta01230:Biosynthesis of amino acids | 4 | 1.45 | 1.4E-01 | 327669, 520638, 539606, 533630 |
| bta00350:Tyrosine metabolism | 3 | 1.09 | 1.5E-01 | 338074, 280762, 281293 |
| bta00260:Glycine, serine and threonine metabolism | 3 | 1.09 | 1.6E-01 | 511957, 533630, 281293 |
| bta04973:Carbohydrate digestion and absorption | 3 | 1.09 | 1.6E-01 | 100336421, 534923, 282868 |
| bta05410:Hypertrophic cardiomyopathy (HCM) | 4 | 1.45 | 1.6E-01 | 521616, 497019, 539969, 280979 |
| bta05034:Alcoholism | 7 | 2.54 | 1.7E-01 | 281385, 512696, 327672, 280762, 281201, 281293, 281202 |
| bta04722:Neurotrophin signaling pathway | 5 | 1.81 | 1.7E-01 | 100034674, 534923, 282162, 512696, 327672 |
| bta05132:Salmonella infection | 4 | 1.45 | 1.8E-01 | 326600, 280979, 327672, 538559 |
| bta05164:Influenza A | 6 | 2.17 | 1.8E-01 | 100048947, 534923, 280979, 282493, 286883, 327672 |
| bta05215:Prostate cancer | 4 | 1.45 | 1.9E-01 | 530315, 534923, 613787, 327672 |
| bta05414:Dilated cardiomyopathy | 4 | 1.45 | 1.9E-01 | 521616, 497019, 539969, 280979 |
| bta04512:ECM-receptor interaction | 4 | 1.45 | 1.9E-01 | 282187, 281530, 523526, 407142 |
| bta05160:Hepatitis C | 5 | 1.81 | 2.0E-01 | 530315, 100048947, 534923, 512405, 327672 |
| bta04380:Osteoclast differentiation | 5 | 1.81 | 2.0E-01 | 534923, 526999, 286883, 327666, 327672 |
| bta05030:Cocaine addiction | 3 | 1.09 | 2.1E-01 | 281385, 280762, 281293 |
| bta04910:Insulin signaling pathway | 5 | 1.81 | 2.1E-01 | 539361, 506083, 534923, 512696, 327672 |
| bta04550:Signaling pathways regulating pluripotency of stem cells | 5 | 1.81 | 2.2E-01 | 281867, 445417, 534923, 327672, 539504 |
| bta04020:Calcium signaling pathway | 6 | 2.17 | 2.3E-01 | 538439, 281969, 282162, 282411, 281750, 282412 |
| bta00480:Glutathione metabolism | 3 | 1.09 | 2.4E-01 | 517724, 615507, 327669 |
| bta05169:Epstein-Barr virus infection | 6 | 2.17 | 2.4E-01 | 280955, 516099, 534923, 507781, 510921, 286883 |
| bta05223:Non-small cell lung cancer | 3 | 1.09 | 2.5E-01 | 530315, 534923, 327672 |
| bta05217:Basal cell carcinoma | 3 | 1.09 | 2.5E-01 | 540830, 445417, 510255 |
| bta05221:Acute myeloid leukemia | 3 | 1.09 | 2.5E-01 | 506083, 534923, 327672 |
| bta04024:cAMP signaling pathway | 6 | 2.17 | 2.6E-01 | 540830, 281701, 534923, 281192, 282162, 327672 |
| bta01210:2-Oxocarboxylic acid metabolism | 2 | 0.72 | 2.7E-01 | 327669, 520638 |
| bta04150:mTOR signaling pathway | 3 | 1.09 | 2.7E-01 | 506083, 534923, 327672 |
| bta04370:VEGF signaling pathway | 3 | 1.09 | 2.7E-01 | 516099, 534923, 327672 |
| bta04921:Oxytocin signaling pathway | 5 | 1.81 | 2.8E-01 | 521616, 539969, 280979, 282162, 327672 |
| bta04660:T cell receptor signaling pathway | 4 | 1.45 | 2.9E-01 | 534923, 281054, 327672, 407098 |
| bta04931:Insulin resistance | 4 | 1.45 | 3.0E-01 | 539361, 506083, 534923, 537062 |
| bta00360:Phenylalanine metabolism | 2 | 0.72 | 3.1E-01 | 280762, 281293 |
| bta05212:Pancreatic cancer | 3 | 1.09 | 3.1E-01 | 530315, 534923, 327672 |
| bta04724:Glutamatergic synapse | 4 | 1.45 | 3.1E-01 | 533760, 327672, 281201, 281202 |
| bta04664:Fc epsilon RI signaling pathway | 3 | 1.09 | 3.3E-01 | 534923, 286883, 327672 |
| bta04520:Adherens junction | 3 | 1.09 | 3.3E-01 | 282637, 280979, 327672 |
| bta00340:Histidine metabolism | 2 | 0.72 | 3.3E-01 | 280762, 281293 |
| bta05412:Arrhythmogenic right ventricular cardiomyopathy (ARVC) | 3 | 1.09 | 3.4E-01 | 521616, 539969, 280979 |
| bta04670:Leukocyte transendothelial migration | 4 | 1.45 | 3.4E-01 | 614055, 512405, 280979, 526999 |
| bta04152:AMPK signaling pathway | 4 | 1.45 | 3.5E-01 | 539361, 506083, 280836, 534923 |
| bta04920:Adipocytokine signaling pathway | 3 | 1.09 | 3.5E-01 | 280836, 534923, 506059 |
| bta05145:Toxoplasmosis | 4 | 1.45 | 3.5E-01 | 534923, 282493, 286883, 327672 |
| bta04340:Hedgehog signaling pathway | 2 | 0.72 | 3.6E-01 | 540830, 510255 |
| bta05220:Chronic myeloid leukemia | 3 | 1.09 | 3.6E-01 | 534923, 512696, 327672 |
| bta04917:Prolactin signaling pathway | 3 | 1.09 | 3.7E-01 | 534923, 512696, 327672 |
| bta04925:Aldosterone synthesis and secretion | 3 | 1.09 | 4.0E-01 | 282162, 282411, 282412 |
| bta04062:Chemokine signaling pathway | 5 | 1.81 | 4.0E-01 | 534923, 512696, 327672, 281201, 281202 |
| bta04260:Cardiac muscle contraction | 3 | 1.09 | 4.1E-01 | 521616, 497019, 539969 |
| bta03010:Ribosome | 4 | 1.45 | 4.1E-01 | 615638, 399560, 508928, 614241 |
| bta04310:Wnt signaling pathway | 4 | 1.45 | 4.3E-01 | 783665, 445417, 534450, 282162 |
| bta04530:Tight junction | 4 | 1.45 | 4.3E-01 | 614055, 534923, 512405, 280979 |
| bta04912:GnRH signaling pathway | 3 | 1.09 | 4.4E-01 | 282162, 286883, 327672 |
| bta04914:Progesterone-mediated oocyte maturation | 3 | 1.09 | 4.6E-01 | 534923, 514174, 327672 |
| bta00983:Drug metabolism - other enzymes | 2 | 0.72 | 4.7E-01 | 533587, 281568 |
| bta05340:Primary immunodeficiency | 2 | 0.72 | 4.7E-01 | 281054, 407098 |
| bta00591:Linoleic acid metabolism | 2 | 0.72 | 4.8E-01 | 503552, 535243 |
| bta05032:Morphine addiction | 3 | 1.09 | 4.8E-01 | 281969, 281201, 281202 |
| bta01130:Biosynthesis of antibiotics | 5 | 1.81 | 4.8E-01 | 281613, 327669, 520638, 539606, 533630 |
| bta04390:Hippo signaling pathway | 4 | 1.45 | 4.9E-01 | 445417, 282637, 510255, 280979 |
| bta04514:Cell adhesion molecules (CAMs) | 4 | 1.45 | 5.0E-01 | 282637, 512405, 282493, 407098 |
| bta05166:HTLV-I infection | 6 | 2.17 | 5.1E-01 | 445417, 515700, 534923, 281148, 282493, 281054 |
| bta01100:Metabolic pathways | 23 | 8.33 | 5.1E-01 | 327669, 508345, 100336421, 503552, 506308, 532724, 539606, 533630, 506059, 515030, 510440, 281482, 511124, 533587, 615819, 535243, 616934, 338074, 520638, 280762, 281568, 504769, 281293 |
| bta04915:Estrogen signaling pathway | 3 | 1.09 | 5.1E-01 | 534923, 512696, 327672 |
| bta03022:Basal transcription factors | 2 | 0.72 | 5.3E-01 | 509259, 510921 |
| bta04723:Retrograde endocannabinoid signaling | 3 | 1.09 | 5.4E-01 | 327672, 281201, 281202 |
| bta04750:Inflammatory mediator regulation of TRP channels | 3 | 1.09 | 5.4E-01 | 535243, 282162, 286883 |
| bta04620:Toll-like receptor signaling pathway | 3 | 1.09 | 5.5E-01 | 534923, 286883, 327672 |
| bta04022:cGMP-PKG signaling pathway | 4 | 1.45 | 5.6E-01 | 282135, 534923, 327672, 281750 |
| bta04930:Type II diabetes mellitus | 2 | 0.72 | 5.6E-01 | 327672, 282411 |
| bta04668:TNF signaling pathway | 3 | 1.09 | 5.6E-01 | 534923, 286883, 327672 |
| bta04080:Neuroactive ligand-receptor interaction | 6 | 2.17 | 5.8E-01 | 538439, 280836, 282135, 533760, 280805, 281750 |
| bta04114:Oocyte meiosis | 3 | 1.09 | 5.8E-01 | 514174, 282162, 327672 |
| bta00330:Arginine and proline metabolism | 2 | 0.72 | 5.9E-01 | 539606, 281293 |
| bta00280:Valine, leucine and isoleucine degradation | 2 | 0.72 | 5.9E-01 | 510440, 338074 |
| bta04919:Thyroid hormone signaling pathway | 3 | 1.09 | 5.9E-01 | 534923, 280979, 327672 |
| bta05142:Chagas disease (American trypanosomiasis) | 3 | 1.09 | 5.9E-01 | 534923, 281054, 327672 |
| bta05152:Tuberculosis | 4 | 1.45 | 6.1E-01 | 534923, 282493, 282162, 327672 |
| bta04923:Regulation of lipolysis in adipocytes | 2 | 0.72 | 6.2E-01 | 535588, 534923 |
| bta04360:Axon guidance | 3 | 1.09 | 6.4E-01 | 533256, 534553, 327672 |
| bta05230:Central carbon metabolism in cancer | 2 | 0.72 | 6.6E-01 | 534923, 327672 |
| bta04210:Apoptosis | 2 | 0.72 | 6.6E-01 | 281662, 534923 |
| bta04144:Endocytosis | 5 | 1.81 | 6.7E-01 | 326600, 530315, 511582, 507781, 511691 |
| bta04068:FoxO signaling pathway | 3 | 1.09 | 6.7E-01 | 530315, 534923, 327672 |
| bta04720:Long-term potentiation | 2 | 0.72 | 6.8E-01 | 282162, 327672 |
| bta05210:Colorectal cancer | 2 | 0.72 | 6.9E-01 | 534923, 327672 |
| bta05211:Renal cell carcinoma | 2 | 0.72 | 6.9E-01 | 534923, 327672 |
| bta04976:Bile secretion | 2 | 0.72 | 7.0E-01 | 407224, 536203 |
| bta05416:Viral myocarditis | 2 | 0.72 | 7.0E-01 | 280979, 282493 |
| bta03320:PPAR signaling pathway | 2 | 0.72 | 7.1E-01 | 537062, 506059 |
| bta04662:B cell receptor signaling pathway | 2 | 0.72 | 7.1E-01 | 534923, 327672 |
| bta05140:Leishmaniasis | 2 | 0.72 | 7.1E-01 | 282493, 327672 |
| bta04115:p53 signaling pathway | 2 | 0.72 | 7.1E-01 | 281530, 282261 |
| bta00590:Arachidonic acid metabolism | 2 | 0.72 | 7.2E-01 | 535243, 504769 |
| bta04612:Antigen processing and presentation | 2 | 0.72 | 7.3E-01 | 282493, 407098 |
| bta05133:Pertussis | 2 | 0.72 | 7.4E-01 | 534553, 327672 |
| bta04932:Non-alcoholic fatty liver disease (NAFLD) | 3 | 1.09 | 7.7E-01 | 539361, 280836, 534923 |
| bta04146:Peroxisome | 2 | 0.72 | 7.7E-01 | 327669, 506059 |
| bta04727:GABAergic synapse | 2 | 0.72 | 7.8E-01 | 281201, 281202 |
| bta05222:Small cell lung cancer | 2 | 0.72 | 7.9E-01 | 534923, 523526 |
| bta04141:Protein processing in endoplasmic reticulum | 3 | 1.09 | 8.0E-01 | 281662, 338067, 530610 |
| bta04922:Glucagon signaling pathway | 2 | 0.72 | 8.1E-01 | 534923, 282162 |
| bta00230:Purine metabolism | 3 | 1.09 | 8.2E-01 | 281613, 281969, 511665 |
| bta05010:Alzheimer's disease | 3 | 1.09 | 8.2E-01 | 281662, 327672, 530610 |
| bta01200:Carbon metabolism | 2 | 0.72 | 8.5E-01 | 327669, 533630 |
| bta04650:Natural killer cell mediated cytotoxicity | 2 | 0.72 | 8.7E-01 | 512696, 327672 |
| bta04270:Vascular smooth muscle contraction | 2 | 0.72 | 8.8E-01 | 538439, 327672 |
| bta04071:Sphingolipid signaling pathway | 2 | 0.72 | 8.8E-01 | 534923, 327672 |
| bta05162:Measles | 2 | 0.72 | 9.2E-01 | 534923, 281054 |
| bta05161:Hepatitis B | 2 | 0.72 | 9.3E-01 | 534923, 327672 |
| bta05206:MicroRNAs in cancer | 3 | 1.09 | 9.3E-01 | 280955, 282094, 281530 |
| bta05202:Transcriptional misregulation in cancer | 2 | 0.72 | 9.5E-01 | 515700, 282261 |
| bta05168:Herpes simplex infection | 2 | 0.72 | 9.7E-01 | 100048947, 282493 |
| bta05016:Huntington's disease | 2 | 0.72 | 9.7E-01 | 788092, 510059 |
| bta05203:Viral carcinogenesis | 2 | 0.72 | 9.8E-01 | 510921, 327672 |
| bta04740:Olfactory transduction | 5 | 1.81 | 1.0E+00 | 510452, 618173, 281701, 282162, 514818 |
| bta00071:Fatty acid degradation | 1 | 0.36 | 1.0E+00 | 506059 |
| bta05014:Amyotrophic lateral sclerosis (ALS) | 1 | 0.36 | 1.0E+00 | 286883 |
| bta00500:Starch and sucrose metabolism | 1 | 0.36 | 1.0E+00 | 100336421 |
| bta03420:Nucleotide excision repair | 1 | 0.36 | 1.0E+00 | 508389 |
| bta04610:Complement and coagulation cascades | 1 | 0.36 | 1.0E+00 | 505574 |
| bta00620:Pyruvate metabolism | 1 | 0.36 | 1.0E+00 | 767889 |
| bta05020:Prion diseases | 1 | 0.36 | 1.0E+00 | 327672 |
| bta00232:Caffeine metabolism | 1 | 0.36 | 1.0E+00 | 503552 |
| bta00053:Ascorbate and aldarate metabolism | 1 | 0.36 | 1.0E+00 | 533587 |
| bta00860:Porphyrin and chlorophyll metabolism | 1 | 0.36 | 1.0E+00 | 533587 |
| bta00052:Galactose metabolism | 1 | 0.36 | 1.0E+00 | 100336421 |
| bta00562:Inositol phosphate metabolism | 1 | 0.36 | 1.0E+00 | 511124 |
| bta01212:Fatty acid metabolism | 1 | 0.36 | 1.0E+00 | 506059 |
| bta05322:Systemic lupus erythematosus | 1 | 0.36 | 1.0E+00 | 282493 |
| bta05012:Parkinson's disease | 1 | 0.36 | 1.0E+00 | 510683 |
| bta04730:Long-term depression | 1 | 0.36 | 1.0E+00 | 327672 |
| bta00240:Pyrimidine metabolism | 1 | 0.36 | 1.0E+00 | 281568 |
| bta05330:Allograft rejection | 1 | 0.36 | 1.0E+00 | 282493 |
| bta00670:One carbon pool by folate | 1 | 0.36 | 1.0E+00 | 505677 |
| bta00300:Lysine biosynthesis | 1 | 0.36 | 1.0E+00 | 520638 |
| bta00310:Lysine degradation | 1 | 0.36 | 1.0E+00 | 520638 |
| bta04120:Ubiquitin mediated proteolysis | 1 | 0.36 | 1.0E+00 | 507781 |
| bta04130:SNARE interactions in vesicular transport | 1 | 0.36 | 1.0E+00 | 613567 |
| bta00270:Cysteine and methionine metabolism | 1 | 0.36 | 1.0E+00 | 508345 |
| bta03430:Mismatch repair | 1 | 0.36 | 1.0E+00 | 508389 |
| bta00061:Fatty acid biosynthesis | 1 | 0.36 | 1.0E+00 | 506059 |
| bta04744:Phototransduction | 1 | 0.36 | 1.0E+00 | 281201 |
| bta05310:Asthma | 1 | 0.36 | 1.0E+00 | 282493 |
| bta04911:Insulin secretion | 1 | 0.36 | 1.0E+00 | 282162 |
| bta05323:Rheumatoid arthritis | 1 | 0.36 | 1.0E+00 | 282493 |
| bta04960:Aldosterone-regulated sodium reabsorption | 1 | 0.36 | 1.0E+00 | 327672 |
| bta04961:Endocrine and other factor-regulated calcium reabsorption | 1 | 0.36 | 1.0E+00 | 511691 |
| bta04672:Intestinal immune network for IgA production | 1 | 0.36 | 1.0E+00 | 282493 |
| bta00650:Butanoate metabolism | 1 | 0.36 | 1.0E+00 | 532724 |
| bta00512:Mucin type O-Glycan biosynthesis | 1 | 0.36 | 1.0E+00 | 615819 |
| bta05320:Autoimmune thyroid disease | 1 | 0.36 | 1.0E+00 | 282493 |
| bta05332:Graft-versus-host disease | 1 | 0.36 | 1.0E+00 | 282493 |
| bta00250:Alanine, aspartate and glutamate metabolism | 1 | 0.36 | 1.0E+00 | 532724 |
| bta05150:Staphylococcus aureus infection | 1 | 0.36 | 1.0E+00 | 282493 |
| bta00760:Nicotinate and nicotinamide metabolism | 1 | 0.36 | 1.0E+00 | 338074 |
| bta04621:NOD-like receptor signaling pathway | 1 | 0.36 | 1.0E+00 | 327672 |
| bta04721:Synaptic vesicle cycle | 1 | 0.36 | 1.0E+00 | 511691 |
| bta05144:Malaria | 1 | 0.36 | 1.0E+00 | 281530 |
| bta05321:Inflammatory bowel disease (IBD) | 1 | 0.36 | 1.0E+00 | 282493 |
| bta04940:Type I diabetes mellitus | 1 | 0.36 | 1.0E+00 | 282493 |
| bta00020:Citrate cycle (TCA cycle) | 1 | 0.36 | 1.0E+00 | 327669 |
| bta03030:DNA replication | 1 | 0.36 | 1.0E+00 | 508389 |
| bta00040:Pentose and glucuronate interconversions | 1 | 0.36 | 1.0E+00 | 533587 |
| bta04950:Maturity onset diabetes of the young | 1 | 0.36 | 1.0E+00 | 524074 |
| bta02010:ABC transporters | 1 | 0.36 | 1.0E+00 | 536203 |
| bta04924:Renin secretion | 1 | 0.36 | 1.0E+00 | 281969 |
| bta04971:Gastric acid secretion | 1 | 0.36 | 1.0E+00 | 282162 |
| bta04070:Phosphatidylinositol signaling system | 1 | 0.36 | 1.0E+00 | 511124 |

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