Molecular basis for residual feed intake in beef cattle

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ABSTRACT: Feed provision is one of the greatest costs of beef production and, with the increasing costs of feed, will remain so for the foreseeable future. Improvement in efficiency has the potential to not only increase profits for cattle producers, but also to decrease the environmental footprint of beef cattle production. Both are important in addressing the challenges of increasing feed costs and land pressure. Residual feed intake (RFI) has increasingly become the measure of choice when evaluating feed efficiency in beef cattle, especially because it is independent of growth and BW. The main inhibitor to adoption of RFI remains the cost and technical difficulty in measuring the trait. This makes RFI a prime candidate for marker-assisted selection because the trait is moderately heritable and DNA or other predictive markers could be used in selection schemes. Although multiple markers have been described over several studies, no major gene affecting RFI has been found. However, a combination of genetic markers, when examined jointly, can explain a large proportion of the genetic variation. Two main barriers remain before full adoption of markers for genetic evaluation and marker-assisted selection can be implemented. First, the genetic interaction of genes affecting RFI on other traits is, as yet, not fully understood. Second the numbers of animals with high quality estimates of RFI remains small. However, current developments indicate that these challenges will soon be overcome.

Key words: beef cattle, genetics, residual feed intake, single nucleotide polymorphism

INTRODUCTION

One way to maximize the profitability of beef cattle production is to minimize the input costs. Feed provision is one of the greatest costs of production (Herd et al., 2003) and, with the increasing costs of feed, will remain so for the foreseeable future. For these reasons, assessing the efficiency of individual animals has been of interest for many years. Residual feed intake \( [\text{RFI}] \) or net feed efficiency (Koch et al., 1963) has been proposed as a measure of efficiency that is independent of growth and BW. Residual feed intake is moderately heritable (Koch et al., 1963; Arthur et al., 2001a; Crews, 2005) and, as such, is a good candidate for genetic improvement. The main inhibition of adoption of selection strategies based on RFI is the difficulty and expense of measuring individual animal BW and feed intake over a period of up to 90 d. This makes the development of predictive genetic markers an attractive alternative to direct measurement on large numbers of animals. This paper reviews the different estimates of animal efficiency and the state of the art in the development and application of genetic markers for RFI.

MEASURING FEED EFFICIENCY

Profitability of a beef operation is determined largely by reduction of input or production costs, especially those associated with feeding, because cattle producers generally cannot control the market prices for their products (Herd et al., 2003). Incorporation of feed efficiency into breeding objectives would increase the genetic potential for animals to have less feed intake while maintaining the same production levels. It has been demonstrated that more efficient cattle have multiple benefits, such as decreased DMI, less manure production, and less emission of methane (Nkrumah et al., 2006; Hegarty et al., 2007).

Extensive research has been done for many decades now on feed energy utilization in cattle. It is apparent that a large portion of ME of any ration is used for maintenance (Pitchford, 2004). However, there is
individual animal variation in maintenance requirements (Johnson et al., 2003), as well as in feed intake (Richardson and Herd, 2004). This lays the basis for improving the efficiency of energy utilization in livestock species.

Over the years, many different measures of feed efficiency have been proposed. Traditionally, efficiency has been defined as a ratio of feed:gain or G:F (Koch et al., 1963; Archer et al., 1999). Some of these ratio traits, such as partial efficiency of growth, feed conversion ratio (FCR), and maintenance efficiency, have been characterized genetically (Archer et al., 1999). However, despite widespread use, these measures are undesirable for genetic improvement purposes because they are often correlated with growth rate (i.e., ADG) or other production traits, such as mature BW (Koots et al., 1994). Also, because selective pressure on the components of a ratio trait is not predictable given that more intensity is usually placed on the component with greater variation (Gunsett, 1984), unit improvement in a ratio trait does not imply an improvement in overall efficiency, such that responses are unpredictable (Crews, 2005).

Koch et al. (1963) suggested an alternative measure that avoids many of the problems listed above, while taking advantage of individual animal variation in maintenance requirement. Residual feed intake, also called net feed intake, was originally defined as the difference obtained when the actual feed intake of an animal is adjusted for growth and maintenance requirements (Koch et al., 1963). Presently, RFI has become an even more desirable measure for characterizing feed efficiency because its definition implicitly allows inclusion of more “energy sinks” besides growth and maintenance, such that comparisons between animals can be made across different segments of production and different stages of development while at the same time still describing individual animal differences (Crews, 2006). This is coupled with the fact that the measure is devoid of any phenotypic correlations with the measurable traits used to estimate it (Basarab et al., 2003).

Typically, through multiple regression analysis, ADG and metabolic BW explain over 60% of the total phenotypic variation in feed intake (Carstens and Tedeschi, 2006). However, other body composition traits, such as ultrasound back fat, have been incorporated in the calculation of RFI to force independence from correlations with them (Basarab et al., 2003; Crews, 2006). Efficient animals consume less feed than expected based on their growth and maintenance requirements such that more efficient animals have a negative RFI value, whereas inefficient animals have a positive RFI value. Accurate measurements of growth (i.e., ADG) and maintenance requirements (estimated using the metabolic mid BW, metabolic BW^{0.75} which is initial BW plus one-half of BW gain on test) are obtained from repeated measurements of BW during a feeding trial. Optimal feeding durations for RFI characterization have been estimated to range between 63 to 84 d depending on the number of days between BW (Archer et al., 1997; Archer and Bergh, 2000; Wang et al., 2006). These repeated records of BW, which should range between 9 and 12 in number, reduce measurement error when estimating gain, as suggested by Koch et al. (1963).

**ECONOMIC IMPLICATIONS OF RFI ESTIMATION**

For accurate estimation of RFI, individual animal feed intake data have to be obtained, and this is only possible through use of expensive equipment. Estimation of pen efficiencies for group-fed animals have been attempted, and several schemes of estimating individual animal efficiency from such intakes have been reported (Guiroy et al., 2001; Tedeschi et al., 2006; Williams et al., 2006). These systems use mathematical models to predict the feed efficiency of an animal from the DM required based on its BW, gain, and feed composition. However, it is only by recording individual animal feed intake that accurate estimation of RFI can be achieved without losing information on inherent differences between individuals.

Even though estimation of RFI is most often done in young growing cattle, the correlation between RFI in growing cattle and in mature cows is significant (Archer et al., 2002). Currently, 75% of total feed costs for production of a beef carcass are used for maintenance of the breeding cow herd. At present, selection strategies are geared toward improving efficiencies of breeding sires because most of the genetic improvement is obtained when sires pass on their characteristics to their offspring (Kahi et al., 2003; Wood et al., 2004).

The total savings from increasing animal efficiency would be considerable, especially for replacement heifers that stay longer in the herd. Selection for greater feed efficiency could potentially result in a reduction of 9 to 10% in maintenance costs for the cow herd, a 10 to 12% reduction in feed intake, a reduction in methane emissions by 25 to 30% (Nkrumah et al., 2006; Hegarty et al., 2007), and a reduction in manure production by 15 to 20% without affecting ADG or mature cow size (Basarab et al., 2002). The economic benefits of selecting for improved efficiency are thus sizeable. It costs about $38 less (given the rising costs of grain and fuel, this figure is bound to increase) to feed an efficient bull compared with an inefficient one for a period lasting 150 d (Crews, 2005).

**PROSPECTS FOR GENETIC SELECTION OF RFI**

Residual feed intake is moderately heritable (Arthur et al., 2001b), with heritability ranging from 0.28 to 0.58 (Koch et al., 1963; Crews et al., 2003). Considerable genetic variation has been demonstrated within populations and across different breeds of cattle tested.
for RFI (Archer and Bergh, 2000; Herd and Bishop, 2000; Basarab et al., 2003). This demonstrates that selection for RFI is possible and benefits of reduced feed intake can be passed on between generations. However, single-trait selection for RFI, a component trait whose underlying economic trait is feed intake, is generally not recommended. This has led to an increased need to define genetic correlations between RFI and other economic traits. Arthur et al. (2001b) reported strong genetic correlations among RFI, FCR, and feed intake, and a weak correlation of RFI with subcutaneous fat (Table 1). Other studies have also associated decreased RFI with a leaner carcass (Basarab et al., 2003; Schenkel et al., 2004). Given these correlations and because there is no association between RFI and growth, it would appear that variation in RFI is a reflection of between-animal differences in biological systems related to efficient feed utilization that are still largely unknown (Crews, 2006).

Richardson et al. (1998) and Arthur et al. (2001a) demonstrated that selection for RFI was effective and the benefits of improved feed efficiency can be achieved in a beef operation. Due to the minimal correlations between RFI and body composition traits, multitrait selection can be undertaken without risk of unfavorable correlated response. Such a selection strategy would be important to ensure that appropriate economic weights are placed on the several component traits in the breeding objective, thereby maximizing the benefits obtainable from selecting for increased feed efficiency. Crews et al. (2006) developed a multitrait economic index that incorporates ADG, RFI, and yearling BW. Carstens and Tedeschi (2006) applied this feedlot profitability index to improve profitability of market progeny. They obtained index values that ranged between 80 and 120. In their study, they compared animals with index values less than 95 with those having greater than 105 and observed a 17% increase in ADG and 9% reduction in feed intake in favor of the more profitable group of animals. These 2 classes of animals had similar yearling BW. This demonstrates that profitability can be maximized at all levels and segments of production, if industry adoption is expedited. However, measurement of the trait requires expensive and specialized equipment, and this has been the major factor hindering wide-scale adoption of feed efficiency as an economically relevant trait and its inclusion in breeding programs. Effective selection could be enhanced if marker-assisted evaluation tools were used. It is estimated that it may cost about $188 per animal to test for individual feed intake (Basarab et al., 2002). This has led to renewed efforts to develop genetic and molecular tools that indirectly measure RFI. Currently, IGF-I tests and a commercial gene test are now in use to augment phenotypic RFI data in Australia.

### CURRENT DEVELOPMENTS IN RFI ADOPTION AND USE

Insulin-like growth factor-I, a hormone that regulates growth and cellular metabolism, has been shown to be associated with increased feed efficiency (Bishop et al., 1989; Stick et al., 1998). The use of this physiological marker as an indirect selection criterion for RFI has been demonstrated (Davis and Simmen, 2006). However, even though decreased IGF-I concentrations are associated with improved efficiency \((r_g = 0.6)\) and IGF-I has a moderate heritability of 0.4 (Moore et al., 2005), IGF-I is correlated with some growth traits (Davis and Simmen, 2006) and carcass measures. To obtain a highly accurate EBV from IGF-I measures alone, much more testing would be required, and because it is an indicator trait, this maximal accuracy will be to the extent of the correlation between IGF-I and RFI.

The use of IGF-I in feed efficiency selection has seen some applications in Australia and the United States. Kahi and Hirooka (2007) also used IGF-I and RFI in a selection strategy resulting in greater accuracy and profitability for Japanese black cattle. However, the extent of the relationship between RFI and IGF-I has been difficult to quantify because conflicting results have been obtained from different studies. Some studies have shown significant correlation (Moore et al., 2005; Kahi and Hirooka, 2007), whereas others found minimal or no correlation (Lancaster et al., 2008). At present, there is increasing doubt that IGF-1 is a reliable indicator that has moderate correlation with RFI, and more investigation to characterize the nature of this relationship will be required before further industry use. If IGF-1 is indeed found to have sufficient correlation

### Table 1. Genetic correlations between residual feed intake (RFI) and production traits

<table>
<thead>
<tr>
<th>Trait</th>
<th>(R_g^1)</th>
<th>Source</th>
</tr>
</thead>
<tbody>
<tr>
<td>Backfat</td>
<td>0.16 to 0.17</td>
<td>Arthur et al., 2001a; Schenkel et al., 2004</td>
</tr>
<tr>
<td>FCR(^2)</td>
<td>0.66 to 0.85</td>
<td>Herd and Bishop, 2000; Arthur et al., 2001a,b; Schenkel et al., 2004</td>
</tr>
<tr>
<td>Fat</td>
<td>0.64 to 0.81</td>
<td>Herd and Bishop, 2000; Arthur et al., 2001a,b; Schenkel et al., 2004</td>
</tr>
<tr>
<td>IMF(^2)/marbling score</td>
<td>−0.44</td>
<td>Crews et al., 2003</td>
</tr>
<tr>
<td>REA(^3)</td>
<td>−0.17</td>
<td>Schenkel et al., 2004</td>
</tr>
<tr>
<td>Methane</td>
<td>0.44</td>
<td>Nkrumah et al., 2006</td>
</tr>
<tr>
<td>Feeding duration</td>
<td>0.43</td>
<td>Lancaster et al., 2005</td>
</tr>
<tr>
<td>Heat production</td>
<td>0.68</td>
<td>Nkrumah et al., 2006</td>
</tr>
</tbody>
</table>

\(^1\)R_g = genetic correlation.

\(^2\)REA = rib-eye area, IMF = intramuscular fat, FI = feed intake, and FCR = feed conversion ratio.
with RFI in multiple populations and breeds of beef
cattle, then it will likely be more useful where RFI data
are available, such that its incorporation in RFI evalu-
ations will increase accuracy of the EBV obtained.

Considerable research is underway to determine the
genetic basis of RFI, and results thus far are encourag-
ing (Arthur and Herd, 2006; Moore et al., 2006; Nkrum-
ah et al., 2007; Sherman et al., 2008a). However, only
a limited number of studies have been published. Bar-
endse et al. (2007) performed a whole-genome associa-
tion study, in which the MegAllele Genotyping Bovine
10K SNP panel was assessed (Hardenbol et al., 2005).
Marker spacing on this chip averaged 325 kbp. The chip
was used to genotype 189 cattle consisting of Angus,
Brahman, Belmont Red, Hereford, Murray Grey, Santa
Gertrudis, and Shorthorn breeds, representing animals
with extreme RFI values and being a subset from a to-
tal population of 1,472 animals. In that study, 161 SNP
were found to be associated ($P < 0.01$) with RFI when
tested individually. The amount of the genetic variance
for RFI explained by the 20 most significant SNP was
76%, whereas subsequent sets of 20 SNP from the 161
progressively explained less variance.

Analysis of SNP locations in the Barendse et al.
(2007) study showed that the significant SNP for RFI
were proportionally represented in micro-RNA motifs,
promoter sequences, or mRNA sequences compared with
the rest of the SNP evaluated. This showed that many
different types of DNA variants may play a role in
RFI variation and any one type was not more im-
portant for RFI than the others. However, there was a
difference in the type of micro-RNA motifs that were in
the flanking SNP sequence compared with the rest of
the SNP. This was not due to different sequence com-
position because the types of promoter elements did
not differ between RFI SNP and the other SNP. This
suggests a signature of regulation unique to RFI. Of
the 161 SNP, 90 contained micro-RNA motifs and 86
contained promoter elements in the sequence flanking
the SNP (Barendse et al., 2007). These nongenic DNA
variants will be important in unraveling the molecular
basis of RFI.

Looking at the functions of the genes harboring the
RFI SNP (intronic and exonic), they found a greater
number of genes (i.e., 34 genes) that contribute to the
background use of energy in the cell, including pro-
cesses such as apoptosis, cell progression, ion channels
and flux, transcription, translation, growth, and devel-
opment. There were only 3 positional candidate genes
involved in appetite and body-mass homeostasis. Elev-
en genes were involved in extracellular matrix and tis-
sue structure including genes involved in muscular and
myotonic dystrophy in humans, cell adhesion, and 2
laminin genes. The authors suggested that these genes
indicate a possible trade-off between feed efficiency and
tissue strength. Nine genes were involved in regulation
of expression such as DNA-binding proteins and signal
transduction proteins. Twenty-eight SNP were in hy-
pothetical or genes with unknown functions and may
provide new or similar functions that have an effect on
RFI.

Whole genome association studies are important for
identifying DNA variants that affect phenotypes, as
shown in other studies in humans (Sladek et al., 2007;
Zeggini and McCarthy, 2007), but there have been fail-
ures in validating results of genome-wide studies (Goris
et al., 2006). Barendse et al. (2007) chose to validate 34
of the 161 SNP in the larger set of animals. Seventy-six
percent of these were validated, 13 SNP at $P < 0.05$
across breeds and 13 that were significant in at least
one of the breeds. The point they emphasized from the
validation was that level of significance or size of effect
were not good predictors of performance of the SNP in
further studies, which are often the criteria used to se-
lect SNP. They found that the consistency of the direc-
tion of effect in different populations is the key factor
to the success of a SNP.

A primary genome scan to identify putative QTL for
RFI was done at the University of Alberta Bovine Ge-
nomics unit using multiple-marker interval mapping in
half-sib families with a random sire model (Nkrumah
et al., 2007). This study used 400 beef cattle steers that
were offspring of 20 Angus, Charolais, or Alberta Hy-
bred bulls. The markers used were 100 microsatellites
and 355 SNP spanning the 29 bovine autosomes. Eight
QTL for RFI were identified across the families with a
chromosome-wise $P < 0.05$ threshold on Bos taurus
autosome (BTA) 1, 5, 7, 8, 12, 16, 17, and 26. Suggest-
ive QTL for RFI with a chromosome-wise $P < 0.10$
threshold were also identified on BTA 2, 14, 18, 19, 20,
21, 24, 28, and 29. The study also looked at genetic and
phenotypic RFI [$RF{I}_{g}$ and $RF{I}_{p}$, respectively (Ken-
nedy et al., 1993)]. Concordance of QTL between $RF{I}_{p}$
and $RF{I}_{g}$ was high, 14 of the RFI QTL were detected
in both $RF{I}_{p}$ and $RF{I}_{g}$. Only 1 suggestive $RF{I}_{g}$ QTL
and 2 suggestive $RF{I}_{p}$ QTL were not detected in the
other RFI measure.

Nkrumah et al. (2007) also looked at QTL for DMI,
FCR, and ADG. Consistent with the fact that there
are genetic correlations among these traits, they found
that there were some QTL for these traits in similar
locations. They concluded that due to these results and
that there are genetic correlations, there will be sev-
eral potential genes that will have pleiotropic effects on
these traits. This conclusion points to the important
issue of investigating the effects of QTL or markers on
other traits when studying the molecular basis of RFI,
so as to avoid unwanted correlated responses when se-
lecting for RFI.

One of the issues with QTL interval mapping is the
large QTL intervals. Because the study by Nkrumah
et al. (2007) was a primary genome scan with a low
marker density (i.e., approximately 16 markers per
chromosome), it is not surprising that the QTL inter-
vals span over an average of 30 cM. To address this,
further studies have fine-mapped QTL on BTA 2, 5,
20, and 29 (Moore et al., 2006; Sherman et al., 2008b).
More SNP were added to these 4 chromosomes for a
total of 423 SNP with an average spacing of 1.01 cM. The position of the QTL changed with the addition of more markers, the biggest change on BTA 5 from 129 cM to 91 cM and the smallest change on BTA 20 from 55 to 56 cM. This narrowed the average interval of the QTL down to 18.25 cM, but this is still a large chromosomal segment. To further refine the QTL location, the individual markers were also analyzed in these regions (Sherman et al., 2008b). Approximately 16 SNP were analyzed surrounding the QTL location, with an average spacing of 0.76 cM or 1,260 kbp. On BTA 2, 5, and 29, one SNP within each QTL region was found with \( P < 0.05 \) and these help pinpoint possible locations for the RFI QTL. Several significant SNP were found on BTA 20, making it unclear where the QTL lies. Notably, the GH receptor (GHR) gene is located within this region. An intronic SNP within the GHR gene had previously been found to be associated with RFI (Sherman et al., 2008a). The SNP in the fine-mapping study were also tested for associations with FCR and DMI. As in the genome scan, some of the markers also showed associations with FCR, DMI, or both FCR and DMI, once again demonstrating the importance of testing SNP for multiple traits, other than the trait of interest.

Sherman et al. (2008a) also looked at several other genes for effects on many economically relevant traits including RFI. These genes included neuropeptide Y, ghrelin, uncoupling proteins 2 (UCP2) and 3 (UCP3), IGF-II, corticotrophin-releasing hormone, cocaine and amphetamine regulated transcript, melanocortin-4 receptor, proopiomelanocortin, and GH. The genes were chosen as candidate genes for their functions in physiological regulation of feed intake, growth, and energy partitioning in animals. Twenty-four SNP were evaluated throughout these genes, but only the SNP in the GHR gene mentioned previously showed a significant allelic substitution effect on RFI (\( P = 0.032 \)). A SNP in the ghrlein and neuropeptide Y introns and another SNP in the promoter region of GHR gene also showed suggestive associations with RFI (\( P < 0.10 \)). Although all these genes have functions that are likely to play a role in feed efficiency, the success rate was low, which illustrates how difficult it is to predict candidate genes at a genome-wide level.

One other study also looked at UCP2 and UCP3 as candidates for affecting RFI (Kolath et al., 2006b). In this study, the mRNA and protein expression levels in Angus steers selected to have high and low RFI were examined. The authors did not find any associations between RFI and expression levels of UCP2 or UCP3. In an earlier study, the same authors also found that the rate of mitochondrial respiration is increased in low RFI steers compared with high RFI steers (Kolath et al., 2006a). To follow up on this they also identified polymorphisms within the mitochondrial genome in the high and low RFI cattle (Kolath et al., 2006b). However, no associations between these polymorphisms and RFI were detected.

### SUMMARY AND CONCLUSIONS

Improvement in feed efficiency has the potential to not only increase profits for cattle producers but to decrease the environmental footprint of beef cattle production. Both are important in addressing the challenges of increasing feed costs and land pressure. Of the currently recognized measures of efficiency, RFI seems to have some advantage because it is independent of growth and mature size.

The main inhibitor to adoption of RFI remains the cost and technical difficulty in measuring the trait. This makes RFI a prime candidate for marker assisted selection because the trait is moderately heritable such that DNA or other predictive markers could be used in selection schemes. However, despite multiple markers having been described over several studies, no major gene affecting RFI has been found, although a combination of genetic markers together can explain a large proportion of the genetic variation. Two main barriers remain before full adoption of markers can be implemented. First, the genetic interaction of genes affecting RFI on other traits is, as yet, not fully understood. Second, the number of animals with high quality estimates of RFI remains small. Most validation data sets that are needed require pooling together groups and populations of animals to obtain the large numbers necessary for the validation. Even among these various data sets and studies, the environmental conditions and genetic background of the animals vary greatly, ranging from Australia to Canada and across breeds including Bos taurus and Bos indicus cattle. These factors make validation of markers for RFI difficult. The establishment of facilities able to measure individual animal feed intake is, however, increasing rapidly in North America, indicating that these barriers will soon be cleared. At the University of Alberta Kinsella ranch, feed intake testing and data collection capacity is increasing from 200 to 400 head in the immediate future, with 1,000 head capacity planned within the next 2 yr. Other industry-based facilities are being established as well. This will provide the large numbers of animals required for discovery and validation of markers, and therefore, increases our prospects of unraveling the molecular basis of RFI in cattle.

### LITERATURE CITED


