Genome-wide association study for residual concentrate intake using different approaches in Italian Brown Swiss

E. Manca, A. Cesarani, L. Falchia, A. S. Atzoria, G. Gaspà, A. Rossoni, N. P. P. Macciotta and C. Dimauro

ABSTRACT
Residual feed intake (RFI) is the most used measure of feed efficiency. However, considering the importance of concentrates in the ration, a new index, the residual concentrate intake (RCI), was here defined. RCI aims to measure the individual efficiency in converting the concentrate into animal products. Brown Swiss young bulls (N = 736) were genotyped at 41,183 loci. Animals were housed in pens equipped with an automatic feeding system able to recognise the animal and record the concentrate intake. The diet consisted of concentrate and hay (ad libitum). The new RCI index was calculated as the residuals of the linear regression of concentrate intake on metabolic live weight and average daily gain. Animals were ranked according to their corrected RCI and divided into low (LRCI) and high phenotypes (HRCI). A low heritability (0.06 ± 0.03) was estimated using only genomics for this new index. Results from multivariate (M-GWAS) and Bayesian (B-GWAS) approaches were combined to identify SNP associated with RCI. The M-GWAS selected 698 SNPs potentially associated, whereas no significant markers were obtained in B-GWAS. Markers in the last approach were ranked according to their posterior inclusion probability and the first 698 were retained. Only SNPs in common between sorted B-GWAS and M-GWAS (N = 11) were considered associated with RCI. A total of 48 candidate genes were retrieved near these SNPs. Most of them were previously reported to be associated with feed efficiency and RFI. The combined use of multivariate and Bayesian techniques allow to identify SNPs associated with the investigated trait.

HIGHLIGHTS
- RCI could be promising to select animals
- 48 candidate genes were found associated with RCI
- Multivariate technique allowed to identify significant SNPs

Introduction
Feed costs contribute to up to 60% of production costs in the dairy cattle industry (Connor 2015). Production costs strongly depend on animal efficiency: feed consumption decrease when animals can efficiently convert feed into milk or body gain (Negussie et al. 2019; Pulina et al. 2020). Among different indexes suggested to evaluate feed efficiency in cattle, the most popular is probably the residual feed intake (RFI) (Van Arendonk et al. 1991; Manafiazar et al. 2013; Berry and Crowley 2013). It is obtained by subtracting the actual from the expected individual intake required by the animal for its maintenance and production. Being RFI by definition independent from production and body weight, animals with low RFI can consume less feed without reducing the production level. RFI has been investigated in beef, dairy, and dual-purpose cattle (Cantalapiedra-Hijar et al. 2018; Kenny et al. 2018; Romanzin et al. 2021).

In ruminants, feed intake can be roughly separated into forage and concentrate based on grains and feedstuffs rich in energy and protein. According to Purcell et al. (2016), the amount of concentrates offered to dairy cattle has increased in the past decades to solve two main problems: to reduce the extent of negative energy balance (NEB) experienced in early lactation, and to allow cows to achieve their potential milk yield. Concentrates and forages can be offered at the same time in a total mixed ratio or separately (Purcell et al.
In the latter situation, the concentrate is supplied using individual concentrate feeders on the barn or in robot milking systems, while forages are offered ad libitum.

Considering the growing importance of concentrates in the ration composition of ruminants (Purcell et al. 2016), a new index to evaluate feed efficiency, the residual concentrate intake (RCI), is defined in the present research. RCI, similarly to RFI, aims to measure individual efficiency in converting the concentrate into animal products (milk or body gain). Being RCI part of RFI, it should assume the same characteristics of independence from animal-related variables and trait heritability. At present, several countries include RFI in their breeding programs (Pryce et al. 2012; Bolormaa et al. 2013; Connor 2015). However, the cost of measuring RFI (or RCI) represents a strong limitation to population-wide selection programs. Genome-wide association study (GWAS) is a useful tool to understand the genetic basis of a trait and, in consequence, also of RCI. This approach is aimed to identify genomic regions associated with genetic variation in a trait and to select genes that could be associated with it. In the present research, a GWAS for RCI in Italian Brown Swiss cattle was developed by using the multivariate approach (M-GWAS) proposed by Manca et al. (2020).

Materials and methods

Data used in this study were obtained from pre-existing databases and therefore the animal care approval was not needed.

Data

A sample of 1,092 Brown Swiss young bulls was considered in the study. Animals arrived at 5–6 months of age at the ANARB (Italian Association of Brown Swiss, Verona, Italy) genetic centre from different commercial herds. Bulls were housed in a quarantine pen for about one month and they were distributed among pens (no more than six bulls/pen). Each pen was equipped with an automatic feeding system able to recognise the animal and to record the concentrate intake. The diet consisted of concentrate and hay. The concentrate was a commercial pelleted mix formulated using grain meals and agro-industrial byproducts (raw chemical composition: 18.0% of CP, 3.2% of fat, 10.1% of crude fibre, 7.6% of ash, and 0.4% of sodium). Hay was administered ad libitum. Animals remained in pens for three months and the body weight (BW) was recorded monthly. After this period, bulls were moved into single pens for the mount training. From the initial 1,092 young bulls, only 736 animals with at least three BW records were considered for further statistical analysis. The RCI phenotypes were calculated as the residuals of a linear regression model of concentrate intake on metabolic live weight and average daily gain (ADG) (Arthur et al. 2005). These residuals were then adjusted according to the following linear model:

$$ RCI_{ijk} = \mu + M_i + Y_j + e_{ijk} $$

where $M$ was the fixed effect of the $i$th birth month (12), $Y$ was the fixed effect of the $j$th birth year (from 2002 to 2013), and $e$ was the random residual (for more details see Macciotta et al. 2015). Animals were ranked according to their corrected RCI and divided into low (LRCI) and high phenotypes (HRCI). The two groups contained an equal number of individuals, 368 bulls each (Manca et al. 2020).

All animals were genotyped by using the Illumina BovineSNP50 BeadChip (Illumina Inc., San Diego, CA, USA). SNP with call rate lower than 99% or minor allele frequency lower than 5% were removed. The remaining missing genotypes were replaced with the most frequent allele at that specific locus. At the end of data editing, 41,183 SNP located on 29 autosomes (mapped on the ARS-UCD1.2 bovine map release) were available for analysis.

Heritability estimation

Heritability was estimated using the following mixed linear model:

$$ y = \mu + Zu + e $$

where $y$ is a vector of RCI (i.e. the values adjusted for month and year of birth, see the above equation), $\mu$ is the overall mean, $Z$ is an incidence matrix relating phenotypes in $y$ to additive genetic effects in $u$ that is a vector of additive animal effects, and $e$ is a vector of random residuals. Since pedigree was not available, the genetic (co)variances structure for $u$ was $u \sim N(0, G \sigma^2_a)$ where $\sigma^2_a$ is the additive genetic variance and $G$ is the genomic relationship matrix (GRM) built according to VanRaden (2008):

$$ G = \frac{MM'}{\sum 2p_j(1-p_j)} $$

where $M$ is the matrix of genotypes centred by twice
the current allele frequencies (\(p\)) estimated for the \(j\)-th SNP.

Variance components and heritability (\(h^2\)) were estimated using GIBBS3F90 software (Misztal et al. 2014) using a total of 100,000 iterations with the first 10,000 discarded as burn-in and saving 1 sample every 10. Post means and standard deviations were calculated using POSTGIBBSF90 software (Misztal et al. 2014).

**The multivariate and Bayesian GWAS**

The method proposed by Manca et al. (2020) was used to develop a multivariate GWAS. In this approach, associated markers were detected by combining the results of two different techniques. In the first, called multivariate GWAS (M-GWAS), data were arranged in a multivariate manner, with animals on the rows and genotypes (coded as 0, 1, and 2) on the columns. This data was submitted to three multivariate techniques: the canonical discriminant analysis (CDA), the discriminant analysis (DA), and the stepwise discriminant analysis (SDA). The algorithm started applying the CDA separately by chromosome. Then the mean and the standard deviation of the absolute value of canonical coefficients (CC) in the 29 canonical functions (CAN, one for each chromosome) were calculated. For each CAN, only markers whose CC's absolute value was greater than the mean plus one standard deviation were retained. The obtained SNPs were then joined, and the SDA was applied to obtain the maximum number of linearly independent markers. The selected SNPs were used as variables to develop a new CDA where both the Mahalanobis boundaries were annotated (Cesarani et al. 2019a; Manca et al. 2020). Moreover, protein–protein interactions (PPI) were carried out using STRING (https://string-db.org).

CDA and DA were successively applied in an iterative procedure. At each run, the number of involved markers was reduced by deleting those with lower CC's absolute value but still keeping the minimum number of SNPs able to separate groups. The procedure stopped when Hotelling's test was still highly significant (\(p\)-value < .001) and, at the same time, the DA correctly assigned all animals to the group of origin.

In the second technique, called Bayesian GWAS (B-GWAS), the BayesR software (Moser et al. 2015) was used. B-GWAS was carried out using a chain length of 50,000 samples, with the first 20,000 ones being discarded as burn-in and saving every 10th sample. In this approach, the effect of each marker is selected from one out of four possible distributions: \(N(0,0\sigma^2_a), N(0,0.0001\sigma^2_a), N(0,0.001\sigma^2_a), N(0,0.01\sigma^2_a)\), where \(\sigma^2_a\) is the additive genetic variance. The posterior inclusion probability (PIP) for each SNP was calculated as the sum of probability to be included in one of the three non-zero distributions (i.e. 0.0001, 0.001, and 0.01). One SNP was declared significant if its PIP was >0.30 (Pasam et al. 2017). Then SNPs were sorted according to their descending PIP value and the first \(x\)-SNPs were selected, where \(x\) was the minimum number of markers selected by the M-GWAS. Finally, SNPs simultaneously detected in the M-GWAS and the sorted list from B-GWAS was considered associated markers and submitted to gene discovery.

**Gene ontology and enrichment**

Different databases (Ensembl, https://www.ensembl.org; NCBI, https://www.ncbi.nlm.nih.gov/genome; genome-browser https://genome.ucsc.edu) were used to retrieve genes mapped in the ARS-UCD1.2 release. All genes with at least one significant marker inside or in the 250k upstream and downstream from their boundaries were annotated (Cesarani et al. 2019a; Manca et al. 2020). Moreover, protein–protein interactions (PPI) were carried out using STRING (https://string-db.org).

**Results and discussion**

Table 1 reports some basic statistics about the bulls investigated in this study. During the trial, which average length was 181.76 ± 35.47 days, each bull was weighted 7 ± 1 times. The average weights at the beginning and at the end of the trial were 230.4 ± 40.47 and 402.33 ± 51.09 kg, respectively. Thus, the average weight increase was 171.91 ± 45.97 kg. Average ADG and RFI were 0.94 ± 0.16 and −0.02 ± 0.30, respectively. Recently, Romanzin et al. (2021) analysed RFI in young Simmental bulls selected

|                             | Mean   | SD    | Min  | Max  |
|-----------------------------|--------|-------|------|------|
| Records                     | 7      | 1     | 4    | 12   |
| Starting weight, kg         | 230.41 | 40.47 | 139  | 427  |
| Ending weight, kg           | 402.33 | 51.09 | 252  | 561  |
| Starting age, day           | 197.74 | 27.14 | 137  | 339  |
| Ending age, day             | 379.50 | 26.42 | 275  | 496  |
| Weight increase, kg         | 171.91 | 45.97 | 50   | 350  |
| Length trial, day           | 181.76 | 35.47 | 52   | 328  |
| Average daily gain, kg      | 0.94   | 0.36  | 0.47 | 1.44 |
| Residual feed intake        | −0.02  | 0.30  | −2.80| 1.50 |
for high growth capacity. These authors reported ADG and RFI values ranging from 0.86 to 2.23 kg and from −2.55 to +1.86 kg DM/day, respectively.

**Heritability estimation**

The estimated $h^2$ was 0.06 ± 0.03, a value that is lower than the estimates reported in the literature for the RFI. Heritability of 0.16 ± 0.03 for RFI was reported by Lu et al. (2015) in dairy cattle using pedigree information. Recently, also Freely et al. (2020) estimated larger values for RFI in heifers (0.25 ± 0.11) and cows (0.16 ± 0.10) of crossbreed animals using the REML approach (i.e. with pedigree information). Li et al. (2020) reported estimates of 0.14 with either a pedigree or genomic model applied to Holstein dairy cows. Anyway, it must be pointed out that the range of heritabilities for RFI is very large: from 0.07 to 0.62 (Berry and Crowley 2013). In our study, pedigree was not available and $h^2$ was estimated using only the $G$ matrix. Heritability estimated using genomics are often lower than those estimated using pedigree (Aldridge et al. 2020; Hidalgo et al. 2020; Cesaran et al. 2021). Moreover, since this study involved Brown Swiss, a selected dairy breed, and selective genotyping strategy (i.e. the genotyped animals were only top bulls) variance components and $h^2$ estimated using only genomic information are likely to be biased (Cesaran et al. 2019b). This is because the heritability of a trait strongly relies on the covariance among relatives and when only genotypes of the best animals are used to estimate variance components these covariances do not reflect the relationships among animals in the whole population.

**Genome-wide association studies**

No significant SNPs (i.e. SNP with a PIP higher than 0.30) were found using the B-GWAS. On the contrary, using the M-GWAS, 698 SNPs were selected as the minimum number of markers able to separate the two considered groups (LRCI and HRCI). Thus, SNPs in B-GWAS were decreasingly sorted according to their PIP and the first 698 markers were considered. A total of 11 SNPs was found in common between the two lists of markers (i.e. sorted B-GWAS and M-GWAS), which have not necessarily the best PIP. Only these markers were considered significantly associated with RCI (Table 2). BTAs 1 and 6 harboured two SNPs, everyone, whereas the remaining seven markers were found in BTAs 7, 12, 17, 22, 23, 24, and 27, respectively.

**Gene–by–gene description**

Candidate genes nearby the associated SNPs are shown in Table 2. A total of 21 and 25 genes were identified using limits of 100 and 205 kb up and downstream the significant SNP position, respectively. Two markers, ARS-BFGL-NGS-104436 on BTA1 and Hapmap42981-BTA-57599 on BTA24, were found inside genes KCNAB1 and MAPRE2, respectively.

The **Potassium Voltage-Gated Channel Subfamily A Member Regulatory Beta Subunit 1 (KCNAB1)** is involved in the regulation of potassium ion transmembrane transport (Majumder et al. 1995). This gene, located on BTA1, was listed among the candidate genes associated with inbreeding in two cattle populations (Brahman and Tropical Composite) by Reverter et al. (2017), who studied the genomic inbreeding depression for climatic adaptation of tropical beef cattle. The same gene was reported to be associated with congenital deafness in Australian Stumpy Tail Cattle dogs (Xu et al. 2021).

The **Microtubule-associated protein RP/EB family member 2 (MAPRE2)** gene, mapped on BTA24, was found to be associated with the first calving interval in buffaloes (de Araujo Neto et al. 2020). It was also reported among 238 genes differentially expressed in a meta-analysis about molecular signatures of muscle growth and composition retrieved from public transcriptomics data (Bazile et al. 2020), and it has been also associated with carcase and growth traits in chicken (Zhang H et al. 2020).

A cluster of seven genes located on BTA27 (ADRB3, BRF2, PROSC, ERLIN2, GOT1L1, RAB11FIP1, ZNF703) and detected in the present study, was found to be associated with ADG in Nellore cattle (Olivieri et al. 2016). In that study, the genomic region harbouring these genes explained 1.56% of the additive genetic variance of ADG. Hardie et al. (2017) found six genes of this cluster associated with RFI in Holsteins. In the same study, ADGRA2 (BTA6) was associated with RFI, whereas MTHFD2L (BTA27) was related to metabolic body weight, a trait used for RFI calculation (Hardie et al. 2017). The **MTHFD2L** gene was reported to be associated also with other economically important traits, such as carcase conformation in Charolaise and Limousine (Purfield et al. 2019), subclinical ketosis in Holstein dairy cows (Nayeri et al. 2019), and resistance to clinical mastitis in Nordic Holstein cattle (Cai et al. 2018).

The **ERLIN2** gene was reported also among the candidate genes associated with RFI in beef cattle through a gene interaction network (Karisa et al. 2013). Moreover, RAB11FIP1, GOT1L1 and ADRB3 genes
Table 2. List of top associated markers and of the candidate genes highlighted as potentially associated with residual concentrate intake in the present study.

| BTA | SNP name               | SNP position, bp | Gene name                       | Acronym | Distance a |
|-----|------------------------|------------------|---------------------------------|---------|------------|
| 1   | ARS-BFGL-NGS-104436    | 111,137,978      | Voltage-gated potassium channel subunit beta-1 | KCNA1B1 | in         |
|     |                        |                  | Signal sequence receptor subunit 3 | SSR3    | <100 kb    |
|     |                        |                  | TCDD inducible poly(ADP-Ribose) polymerase | TIPARP  | <250 kb    |
|     | ARS-BFGL-NGS-4700      | 142,286,534      | Uromodulin like 1               | UMODL1  | <100 kb    |
|     |                        |                  | C2 domain-containing protein 2   | C2CD2   | <100 kb    |
|     |                        |                  | Zinc finger and BTB domain containing 21 | ZBTB21  | <100 kb    |
|     |                        |                  | Receptor interacting serine/threonine kinase 4 | RIPK4   | <250 kb    |
|     |                        |                  | PR/SET domain 15                | PRDM15  | <250 kb    |
| 6   | Hapmap43045-BTA-76998  | 88,980,880       | C-X-C motif chemokine ligand 3   | CXCL3   | <100 kb    |
|     |                        |                  | Chemokine (CXC motif) ligand 1   | CXCL1   | <100 kb    |
|     |                        |                  | Methylpentahydrofolate dehydrogenase (NADP+ dependent) 2 like | MTHFD2L | <250 kb    |
|     |                        |                  | C-X-C motif chemokine ligand 8   | CXCL8   | <250 kb    |
|     |                        |                  | C-X-C motif chemokine ligand 5   | CXCL5   | <100 kb    |
|     |                        |                  | C-X-C motif chemokine ligand 2   | CXCL2   | <100 kb    |
|     | BTB-01306168           | 111,429,024      | Prominin 1                      | PROM1   | <250 kb    |
| 7   | ARS-BFGL-NGS-29738     | 60,120,094       | Transmembrane anterior posterior transformation 1 | TAPT1  | <100 kb    |
| 12  | ARS-BFGL-NGS-21526     | 10,851,132       | Proctochelin 8                   | PCDH8   | <100 kb    |
|     |                        |                  | Chondromodulin                   | CNMD    | <250 kb    |
|     |                        |                  | Olfactomedin 4                   | OLFM4   | <250 kb    |
| 17  | Hapmap59406-rs29026470 | 34,902,455       | Bardet-Biedl syndrome 12         | BBS12   | <100 kb    |
|     |                        |                  | Centrin 4                        | CETN4   | <100 kb    |
|     |                        |                  | Interleukin 21                   | IL2I    | <250 kb    |
|     |                        |                  | Spermatogenesis associated 5     | SPATAS  | <250 kb    |
|     |                        |                  | Nudix hydrolase 6                | NUDT6   | <100 kb    |
|     |                        |                  | Fibroblast growth factor 2       | FGF2    | <100 kb    |
| 22  | Hapmap44225-BTA-28287  | 57,017,818       | Rabenosyn, RAB effector         | RBSN    | <250 kb    |
|     |                        |                  | Mitochondrial ribosomal protein 52S | MRPS25  | <250 kb    |
|     |                        |                  | Nuclear receptor subfamily 2 group C member 2 | NRRC2  | <250 kb    |
|     |                        |                  | Peroxisome proliferator activated receptor gamma | PPARG  | <250 kb    |
|     |                        |                  | Synapsin II                      | SYN2    | <100 kb    |
|     |                        |                  | TIMP metalloepidase inhibitor 4  | TIMP4   | <100 kb    |
| 23  | ARS-BFGL-NGS-39327     | 48,634,859       | Coagulation factor XIII A chain | F13A1   | <250 kb    |
|     |                        |                  | Lymphocyte antigen 86            | LY86    | <100 kb    |
| 24  | Hapmap42981-BTA-57599  | 29,634,859       | Microtubule associated protein RP/EB family member 2 | MAPRE2 | <250 kb    |
|     |                        |                  | Dystrobrevin alpha               | DTNA    | <250 kb    |
|     |                        |                  | Zinc finger protein 397          | ZNF397  | <250 kb    |
|     |                        |                  | Zinc finger and SCAN domain containing 30 | ZSCAN30 | <250 kb    |
| 27  | ARS-BFGL-NGS-111566    | 32,967,390       | Zinc finger protein 703          | ZNF703  | <100 kb    |
|     |                        |                  | ER lipid raft associated 2        | ERLN2   | <100 kb    |
|     |                        |                  | Pyridoxal phosphate binding protein | PLPBP   | <100 kb    |
|     |                        |                  | Adhesion G protein-coupled receptor A2 | ADGR2A  | <250 kb    |
|     |                        |                  | BRF2 RNA polymerase III transciption initiation factor subunit | BRF2   | <250 kb    |
|     |                        |                  | RAB11 family interacting protein 1 | RAB11FIP1 | <250 kb    |
|     |                        |                  | Glutamic-oxaloacetic transaminase 1 like 1 | GALT1L1 | <250 kb    |
|     |                        |                  | Adrenoceptor beta 3              | ADRB3   | <250 kb    |

*Distance from the significant SNP: in = the SNP was inside the gene; <100 kb = the SNP was from 1 to 100 kb upstream or downstream from the gene; <250 kb = the SNP was from 101 to 250 kb upstream or downstream from the gene.

were found to be related to fat yield in Canadian Holsteins (Li et al. 2010). Hu et al. (2010), reported that ADRB3 is involved in the mobilisation and utilisation of energy in cattle. In fact, this gene was associated with intramuscular fat content and fatty acid composition in pigs (Xue et al. 2016) and with growth traits (i.e. birth weight, growth rate until weaning, and carcass composition) in Merino sheep (Forrest et al. 2003).

Some other interesting genes already associated in cattle with RFI were flagged as significant in this study. The F13A1 gene, located on BTA23, was reported to be associated with RFI by Zhang F et al. (2020), who performed a GWAS on multiple beef cattle breeds. This gene has been also associated with mastitis resistance in Nordic Holstein (Cai et al. 2018). These authors analysed differentially expressed genes in udders and reported that this gene is involved in complement and coagulation cascades. de Lima et al. (2016) carried out a GWAS on Nellore cattle and they associated the TIPARP gene with RFI, suggesting its possible role as a regulatory factor. This gene, located on BTA1, was also reported as a candidate gene for valeric acid in a GWAS for methane emission and ruminal volatile fatty acids using Holstein cattle sequence data (Sarghale et al. 2020). The PCDH8 gene
was recently associated with RFI, residual gain, and feed efficiency in French beef cattle (Taussat et al. 2020). Another gene already associated with feed efficiency in beef cattle and highlighted also in the present study was the DTNA gene. This was reported to be associated with residual ADG by Serão et al. (2013), and with RFI by Chen et al. (2011). Interestingly, the HTR4 gene was highlighted by Yao et al. (2013) in a random forest carried out to identify additive and epistatic SNPs associated with RFI in dairy cattle.

Other genes, even if not directly related to RFI, were reported to be associated with other meat or growth traits related to this phenotype. The ABCG1, located on BTA1, has been associated with ADG in a GWAS carried out on Hereford cattle (Seabury et al. 2017); this gene has also a role in adiposity and fat mass growth in humans and mice (Frisdal et al. 2015). Another gene already associated with ADG, even if in pigs, and also highlighted in the present study is the OLFM4 gene, located on BTA12. Onteru et al. (2013) associated this gene with ADG in pigs through GWAS, whereas Liu et al. (2018) associated the gene with RFI in broilers by using a differential expression analysis.

As far as cattle breeds were concerned, the OLFM4 gene has been also associated with milking speed in Brown Swiss cattle (Kramer et al. 2014) and with coat colour in Vrindavani cattle (Chhotaray et al. 2021). Continuing with the genes already related to growth traits, Lindholm-Perry et al. (2020) recently found the LY86 gene among the genes differentially expressed comparing cohorts of beef steers based on different feed intakes. The ZNF397 gene was found to be significant in gene expression analyses carried out comparing two groups of animals, high-marbling and low-marbling, of Hawoo cattle breed (Lim et al. 2013). Furthermore, its protein is overexpressed in the spermatozooa of high fertile bullock bulls compared to low fertile bulls (Muhammad Aslam et al. 2019). The TIMP4 gene has been found over-expressed in the double-muscled foetuses, compared to normal ones (Hocquette et al. 2007), suggesting a possible role in the muscle development and the animals’ growth; in another study, its mRNA expression remained constant in Longissimus dorsi muscle associated with different stages of intramuscular adipose tissue development (Roberts et al. 2015). The TAP1 gene was reported to be associated with carcass weight and with eviscerated weight, even if in Beijing-You chickens (Liu et al. 2013). The NR2C2 gene was reported among the genes downregulated in the low plane compared to the high plane of nutrition in Angus x Simmental beef cows (Moisá et al. 2015). Thus, its role in energy mobilisation, and therefore a connection with growth traits and RFI, could be supposed. The other three genes found in the present study (RIPK4, PRDM15, and C2CD2) were reported to be associated with the development of loin in Charolaise (Doyle et al. 2020). Two of these genes (PRDM15 and C2CD2) have been also associated with milk yield in Portuguese Holstein cattle (Silva et al. 2020). BBS12 gene has been associated with pure meat weight, foreshank weight, and silver-side weight in Chinese Simmental beef cattle (Chang et al. 2019). Also, MRPS25 was already associated with meat traits, even if in sheep. In particular, according to Bolormaa et al. (2016), this gene is associated with several meat traits. It influences retail colour and increases myoglobin and wet iron contents in muscle; moreover, it increases meat tenderness, decreases pH level, and it influences other important meat traits, such as eye muscle area and eye muscle depth, glycosgen, isocitrate dehydrogenase activity and polyunsaturated fatty acids level (Bolormaa et al. 2016). ZSCAN30 has been associated with first calving interval in buffaloes (de Araujo Neto et al. 2020).

Five genes belonging to the CXC family of chemokines (CXCL1, CXCL2, CXCL3, CXCL5, CXCL8) were flagged as significant genes on BTA 6. This family is involved in the immune response: CXCL1 and CXCL2 have an important role in immune defense because they modulate the leukocyte infiltration (Sharifi et al. 2018), CXCL3 is responsible for the constitutive chemotactic activity of bovine milk for neutrophils (Rainard et al. 2008), whereas CXCL8 plays an important role in a wide range of bovine diseases (Widdison and Coffey 2011). Mukibi et al. (2019) found CXCL2 among the differently expressed genes between Charolaise steers with high and low ADG, and CXCL3 associated with ADG in Angus, Charolaise, and Kinsella composite populations. Also, the IL21 gene was reported to be associated with immune system response and it has been reported as significant in an FST analysis between selected and conserved Polish Red cattle (Gurgul et al. 2019). Other five genes (BBS12, CETN4, SPATAS, NUDT6, and FGF2), mapped in the regions highlighted in this study and related to the immune system in cattle, have been associated with somatic cell count in seven GWAS on different populations of dairy cows (Chen et al. 2015). FGF2 is involved in embryonic mortality in cattle (Khatib et al. 2008), probably because of its role in the stimulation of the interferon-γ which plays a regulating role in the establishment and maintenance of pregnancy in ruminants. (Michael et al. 2006). Another gene associated with reproductive traits found in this study is the UMODL1 gene, which is
involved in the regulation of ovarian follicle development (Grigoletto et al. 2018).

**Gene enrichment and protein–protein interaction (PPI)**

When genes were divided according to their molecular function, five different classes were observed (Table 3). The highlighted classes were binding (23 genes, 47.9% on the total), molecular function regulator (13 genes, 27.1% on the total), catalytic activity (eight genes, 16.7% on the total), molecular transducer activity (three genes), and transporter activity (two genes). The clustering of genes according to the different cellular components is shown in Table 4. Three clusters were obtained: cellular anatomical entity (31 genes), intracellular (20 genes), and protein-containing complex (four genes). When looking at the genes divided according to the biological process they are involved in, 12 different clusters could be observed (Table 5). The three largest classes were cellular process (30 genes, 62.5% on the total), biological regulation (24 genes, 50% on the total), and metabolic process (15 genes, 31.3% on the total). The other highlighted classes grouped 13 or less genes (Table 5).

PPI was investigated for the 48 candidate genes of the present study (Figure 1). The PPI showed more interactions than expected: 55 edges identified (average node degree of 2.34) compared to the nine expected. The $p$-value of the PPI enrichment was lower than 1e$^{-16}$. A big cluster with nine genes (IL21, FGF2, PROM1, CXCL6, GRO1, CXCL8, CXCL3, CXCL2, and OLFM4) already associated with the immune system in the gene-by-gene description (see above) could be observed. A mini-cluster with three genes (ADRB2, ADRB3, and HTR4), previously reported to be associated with RFI in cattle (Yao et al. 2013; Hardie et al. 2017) was also highlighted. Another cluster with six genes (GOT1L1, ZNF703, ERLIN2, PROSC, GPR124, and RAB11FIP1) was observed: some of these genes (GOT1L1, ZNF703, ERLIN2, PROSC, and RAB11FIP1) were already associated with ADG in Nellore and with RFI in Holstein.

**Conclusions**

A novel index, the RCI, was defined to identify efficient and inefficient individuals in converting concentrate into animal products. The GWAS with a Bayesian approach did not highlight any significant marker. However, the use of two complementary approaches of GWAS allowed to select a restricted number of markers, which are more likely to be associated with the investigated trait. When the B-GWAS was combined with the M-GWAS, 11 significantly associated markers and 48 candidate genes were found. Most of them were previously obtained by other authors in GWAS developed for RFI and feed efficiency in general. Moreover, the selected genes were clustered in five different groups according to their molecular function, and, based on cellular components, three clusters were obtained. These results suggest that,
Table 5. Genes divided according to the biological process they are involved in.

| Biological process                                | GO term    | N  | % on total | Genes                                                                                                                                 |
|---------------------------------------------------|------------|----|------------|---------------------------------------------------------------------------------------------------------------------------------------|
| Biological adhesion                               | GO: 0022610|  1 | 2.10%      | PCDH8                                                                                                                                |
| Biological regulation                             | GO: 0065007| 24 | 50.00%     | CXCL3, ZNF397, F13A1, PRMD15, ZSCAN30, KCNAB1, FGF2, ADRB3, ERLIN2, TAPT1, ZNF703, PPARG, CXCL8, CNMD, NUDT6, HTR4, MAPRE2, SYN2, NR2C2, ADRB2, ZBTB21, ABCG1, ADGRA2, TIMP4 |
| Cellular process                                   | GO: 0009987| 30 | 62.50%     | CXCL3, ZNF397, F13A1, RAB11FIP1, PRDM15, ZSCAN30, KCNAB1, GOT1L1, FGF2, ADRB3, PCDH8, ERLIN2, TAPT1, DTNA, ZNF703, PPARG, MTHFD2L, CXCL8, CNMD, NUDT6, HTR4, MAPRE2, SYN2, BRF2, NR2C2, ADRB2, ZBTB21, ADGRA2, TIMP4, CETN4 |
| Developmental process                              | GO: 0032502|  5 | 10.40%     | FGF2, PPARG, CNMD, NR2C2, ADGRA2                                                                                                      |
| Immune system process                              | GO: 0002376|  2 | 4.20%      | CXCL3, CXCL8                                                                                                                         |
| Interspecies interaction between organisms         | GO: 0044419|  2 | 4.20%      | CXCL3, CXCL8                                                                                                                         |
| Localisation                                       | GO: 0051179|  8 | 16.70%     | CXCL3, RAB11FIP1, KCNAB1, FGF2, TAPT1, CXCL8, MAPRE2, SYN2                                                                         |
| Locomotion                                         | GO: 0040011|  3 | 6.30%      | CXCL3, FGF2, CXCL8                                                                                                                   |
| Metabolic process                                  | GO: 0008152| 15 | 31.30%     | ZNF397, F13A1, PRDM15, ZSCAN30, KCNAB1, GOT1L1, FGF2, ERLIN2, ZNF703, PPARG, MTHFD2L, BRF2, NR2C2, ZBTB21, TIMP4                            |
| Multicellular organismal process                   | GO: 0051704|  7 | 14.60%     | F13A1, FGF2, ADRB3, CNMD, NR2C2, ADRB2, ADGRA2                                                                                         |
| Response to stimulus                               | GO: 0050896| 13 | 27.10%     | CXCL3, F13A1, FGF2, ADRB3, ERLIN2, PPARG, CXCL8, CNMD, NUDT6, HTR4, ADRB2, ADGRA2, TIMP4                                           |
| Signaling                                          | GO: 0023052| 13 | 27.10%     | CXCL3, FGF2, ADRB3, ERLIN2, DTNA, PPARG, CXCL8, CNMD, NUDT6, HTR4, SYN2, ADRB2, ADGRA2                                             |

Figure 1. Protein–protein interaction (PPI) was carried out using STRING for the 48 candidate genes.
even though referred to as a part of the daily intake, 
RCI could be a promising index to select animals that 
better convert concentrates into animal products.

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ORCID

A. Cesarani http://orcid.org/0000-0003-4637-8669
A. S. Atzori http://orcid.org/0000-0001-5504-9459
G. Gaspa http://orcid.org/0000-0001-5504-9459
M. Aldridge MN, Vandenplas J, Bergsma R, Calus MP. 2020. 
Variance estimates are similar using pedigree or genomic 
relationships with or without the use of metafounders or 
the algorithm for proven and young animals. J Anim Sci. 
98(3):skaa019.

Arthur PF, Herd RM, Wilkins JF, Archer JA. 2005. Maternal 
productivity of Angus cows divergently selected for post-
weaning residual feed intake. Aust J Exp Agric. 45(8): 
985–993.

Bazile J, Jaffrezic F, Dehais P, Reichstadt M, Klopp C, Laloé D, 
Bonnet M. 2020. Molecular signatures of muscle growth 
and composition deciphered by the meta-analysis of age-
related public transcriptomics data. Physiol Genomics. 
52(8):322–332.

Berry DP, Crowley JJ. 2013. Cell biology symposium: genetics 
of feed efficiency in dairy and beef cattle. J Anim Sci. 
91(4):1594–1613.

Bolormaa S, Hayes BJ, van der Werf JH, Pethick D, Goddard 
ME, Daetwyler HD. 2016. Detailed phenotyping identifies 
genes with pleiotropic effects on body composition. BMC 
Genomics. 17(1):224–221.

Bolormaa S, Pryce JE, Kemper K, Savin K, Hayes BJ, Barendse 
W, Zhang Y, Reich CM, Mason BA, Bunch RJ, et al. 2013. 
Accuracy of prediction of genomic breeding values for 
residual feed intake and carcass and meat quality traits in 
Bos taurus, Bos indicus, and composite beef cattle. J Anim 
Sci. 91(7):3088–3104.

Cai Z, Guldbrandtsen B, Lund MS, Sahana G. 2018. Prioritizing 
candidate genes post-GWAS using multiple sources of 
data for mastitis resistance in dairy cattle. BMC Genomics. 
19(1):656–611.

Cantalapiedra-Hijar G, Abo-Ismail M, Carstens GE, Guan LL, 
Hegarty R, Kenny DA, McGee M, Plastow G, Relling A, 
Ortigues-Marty I. 2018. Review: Biological determinants of 
between-animal variation in feed efficiency of growing 
beef cattle. Animal. 12(2):s321–s335.

Cesaran A, Biffani S, García A, Lourenço D, Bertolini G, Neglia 
G, Miształ I, Macciotta NPP. 2021. Genomic investigation of 
milk production in Italian buffalo. Ital J Anim Sci. 20(1): 
539–547.

Cesaran A, Pocmíl I, Macciotta NPP, Fragomeni BO, Miształ I, 
Lourenço DA. 2019b. Bias in heritability estimates from 
genomic restricted maximum likelihood methods under 
different genotyping strategies. J Anim Breed Genet. 
136(1):40–50.

Cesaran A, Sechi T, Gaspa G, Usai MG, Sorbolini S, Macciotta 
NPP, Carta A. 2019a. Investigation of genetic diversity and 
selection signatures between Sarda and Sardinian 
Ancestral black, two related sheep breeds with evident 
morphological differences. Small Ruminant Res. 177:68–75.

Chang T, Wei J, Wang X, Miao J, Xu L, Zhang L, Gao X, Chen 
Y, Li J, Gao H. 2019. A rapid and efficient linear mixed 
model approach using the score test and its application to 
GWAS. Livest Sci. 220:37–45.

Chen X, Cheng Z, Zhang S, Walrond L, Wathes DC. 2015. 
Combining genome wide association studies and differential 
gene expression data analyses identifies candidate 
genesis affecting mastitis caused by two different pathogens 
in the dairy cow. OJAS. 05(04):358–393.

Chen Y, Gondo C, Quinn K, Herd RM, Parnell PF, Vanselow B. 
2011. Global gene expression profiling reveals genes 
expressed differentially in cattle with high and low residual 
feed intake. Anim Genet. 42(S):475–490.

Chhotaray S, Panigrahi M, Bhushan B, Gaur GK, Dutt T, Mishra 
BP, Singh RK. 2021. Genome-wide association study reveals 
genies crucial for coat color production in Vrindavani 
cattle. Livest Sci. 247:104476.

Connor EE. 2015. Invited review: improving feed efficiency in 
dairy production: challenges and possibilities. Animal. 9(3): 
395–408.

d de Araujo Neto FR, Takada L, Dos Santos DJA, Aspilcueta-
Borquis RR, Cardoso DF, do Nascimento AV, Leão KM, de 
Oliveria HN, Tonhati H. 2020. Identification of genomic 
regions related to age at first calving and first calving 
interval in water buffalo using single-step GBLUP. Reprod 
Domest Anim. 55(11):1565–1572.

d de Lima AO, de Oliveira PSN, Tizioo Pc PSN, Afonso J, 
Somavilla Al Diniz WJS, da Silva Jv Rocha MIP, Mudadu Ma 
Coutinho L, Regitano LDA. 2016. Association analyses 
pointed the TIPARP as a potential candidate gene influenc-
ing residual feed intake variation in Nellore cattle. 
Proceedings of the 1st International Meeting of Advances 
in Animal Science; Jun 8–10; Jaboticabal, Brazil.

Doyle JL, Berry DP, Veerkamp RF, Carthy TR, Evans RD, Walsh 
SW, Purfield DC. 2020. Genomic regions associated with 
muscularity in beef cattle differ in five contrasting cattle 
breeds. Genet Sel. Evol. 52(1):2.

Forrest RH, Hickford JGH, Hogan A, Frampston C. 2003. 
Polyorphism at the ovine beta3-adrenergic receptor 
locus: associations with birth weight, growth rate, carcass 
composition and cold survival. Anim Genet. 34(1):19–25.

Freitly HC, Kuehn LA, Thallman RM, Snelling WM. 2020. 
Heritability and genetic correlations of feed intake, body
weight gain, residual gain, and residual feed intake of beef cattle as heifers and cows. J Anim Sci. 98(1):sk2394.

Frisdal E, Le Lay S, Hooton H, Poupel L, Olivier M, Allili R, Plengpanich V, Villard EF, Gilbert S, Lhomme M, et al. 2015. Adipocyte ATP-binding cassette G1 promotes triglyceride storage, fat mass growth, and human obesity. Diabetes. 64(3):840–855.

Grigoletto L, Mattos EC, Baldi F, Eler JP, Baruselli P, Ferraz JBS. 2018. Genome-wide association study for anti-Müllerian hormone in Nellore cattle. Proceedings of the World Congress on Genetics Applied to Livestock Production, 290.

Gurgul A, Jasieczuk I, Semik-Gurgul E, Szmatała T, Majewska A, Sosin-Bzducha E, Bugno-Poniewierska M. 2019. Diversifying selection signatures among divergently selected subpopulations of Polish Red cattle. J Appl Genet. 60(1):87–95.

Hardie LC, VandeHaar MJ, Tempelman RJ, Weigel KA, Armentano LE, Wiggins GR, Veerkamp RF, de Haas Y, Coffey MP, Connor EE, et al. 2017. The genetic and biological basis of feed efficiency in mid-lactation Holstein dairy cows. J Dairy Sci. 100(11):9061–9075.

Hidalgo J, Tsuruta S, Lourenco D, Masuda Y, Huang Y, Gray KA, Misztal I. 2020. Changes in genetic parameters for fitness and growth traits in pigs under genomic selection. J Anim Sci. 98(2):skaa032.

Hocquette J, Lehnert S, Barendse W, Cassar-Malek I, Picard B. 2007. Recent advances in cattle functional genomics and its application to beef quality. Animal. 1(1):159–173.

Hu J, Zhou H, Smyth A, Luo Y, Hickford JG. 2010. Polymorphism of the bovine ADRB3 gene. Mol Biol Rep. 37(7):3389–3392.

Karisa BK, Thomson J, Wang Z, Stothard P, Moore SS, Plastow GS. 2013. Candidate genes and single nucleotide polymorphisms associated with variation in residual feed intake in beef cattle. J Anim Sci. 91(8):3502–3513.

Kenny DA, Fitzsimons C, Waters SM, McGee M. 2018. Invited review: improving feed efficiency of beef cattle – the current state of the art and future challenges. Animal. 12(9):1815–1826.

Khattib H, Maltecca C, Monson RL, Schutzkus V, Wang X, Rutledge JJ. 2008. The fibroblast growth factor 2 gene is associated with embryonic mortality in cattle. J Anim Sci. 86(9):2063–2067.

Kramer M, Erbe M, Seefried FR, Gredler B, Bapst B, Bieber A, Simianer H. 2014. Accuracy of direct genomic values for functional traits in Brown Swiss cattle. J Dairy Sci. 97(3):1774–1781.

Li B, VanRaden PM, Guduk E, O’Connell JR, Null DJ, Connor EE, VandeHaar MJ, Tempelman RJ, Weigel KA, Cole JB. 2020. Genomic prediction of residual feed intake in US Holstein dairy cattle. J Dairy Sci. 103(3):2477–2486.

Li H, Wang Z, Moore SS, Schenkel FS, Stothard P. 2010. Genome-wide scan for positional and functional candidate genes affecting milk production traits in Canadian Holstein Cattle. Proceedings of the 9th World Congress on Genetics Applied to Livestock Production; Leipzig, Germany.

Lim D, Lee SH, Kim NK, Cho YM, Chai HH, Seong HH, Kim H. 2013. Gene co-expression analysis to characterize genes related to marbling trait in Hanwoo (Korean) cattle. Asian Australas J Anim Sci. 26(1):19–29.

Lindholm-Perry AK, Freely HC, Oliver WT, Rempel LA, Keel BN. 2020. Genes associated with body weight gain and feed intake identified by meta-analysis of the mesenteric fat from crossbred beef steers. PLOS One. 15(1):e0227154.

Liu J, Liu R, Wang J, Zhang Y, Xing S, Zheng M, Cui H, Li Q, Li P, Cui X. 2018. Exploring genomic variants related to residual feed intake in local and commercial chickens by whole genomic resequencing. Genes. 9(2):57.

Liu R, Sun Y, Zhao G, Wang F, Wu D, Zheng M, Chen J, Zhang L, Hu Y, Wen J. 2013. Genome-wide association study identifies loci and candidate genes for body composition and meat quality traits in Beijing-You chickens. PLOS One. 8(4):e61172.

Lu Y, VandeHaar MJ, Spurluck DM, Weigel KA, Armentano LE, Staples CR, Connor EE, Wang Z, Bello NM, Tempelman RJ. 2015. An alternative approach to modeling genetic merit of feed efficiency in dairy cattle. J Dairy Sci. 98(9):6535–6551.

Macciotta NPP, Gaspa G, Bomba L, Vicario D, Dimauro C, Cellessi M, Ajmone-Marsan P. 2015. Genome-wide association analysis in Italian Simmental cows for lactation curve traits using a low-density (7K) SNP panel. J Dairy Sci. 98(11):8175–8185.

Majumder K, De Biasi M, Wang Z, Wible BA. 1995. Molecular cloning and functional expression of a novel potassium channel β-subunits from human atrium. FEBS Lett. 361(1):13–16.

Manafazar G, McFadden T, Goonewardene L, Okine E, Basarab J, Li P, Wang Z. 2013. Prediction of residual feed intake for first-lactation dairy cows using orthogonal polynomial regression. J Dairy Sci. 96(12):7991–8001.

Manca E, Cesarani A, Gaspa G, Sorbolini S, Macciotta NPP, Dimauro C. 2020. Use of the multivariate discriminant analysis for genome-wide association studies in cattle. Animals. 10(8):1300.

Michael DD, Alvarez IM, Ocon OM, Powell AM, Talbot NC, Johnson SE, Ealy AD. 2006. Fibroblast growth factor-2 is expressed by the bovine uterus and stimulates interferon-τ production in bovine trophectoderm. Endocrinology. 147(7):3571–3579.

Misztal I, Tsuruta S, Lourenco DAL, Aguilar I, Legarra A, Vitezica Z. 2014. Manual for BLUPF90 family of programs. [accessed 2020 Sep]. http://nce.ads.uga.edu/wiki/lib/exe/fetch.php?media=blupf90_all7.pdf

Moisà SJ, Shike DW, Shoup L, Rodriguez-Zas SL, Loor JJ. 2015. Maternal plane of nutrition during late gestation and weaning age alter angus × simmental offspring longissimus muscle transcriptome and intramuscular fat. PLOS One. 10(7):e0131478.

Moser G, Lee SH, Hayes BJ, Goddard ME, Wray NR, Visscher PM. 2015. Simultaneous discovery, estimation and prediction analysis of complex traits using a Bayesian mixture model. PLOS Genet. 11(4):e1004969.

Muhammad Aslam MK, Kumaresan A, Yadav S, Mohanty TK, Datta TK. 2019. Comparative proteomic analysis of high- and low-fertile buffalo bull spermatozoa for identification of fertility-associated proteins. Reprod Domest Anim. 54(5):786–794.

Mukiibi R, Vinsky M, Keogh K, Fitzsimmons C, Stothard P, Waters SM, Li C. 2019. Liver transcriptome profiling of beef steers with divergent growth rate, feed intake, or
metabolic body weight phenotypes. J Anim Sci. 97(11): 4386–4404.
Nayeri S, Schenkel F, Fleming A, Kroezen V, Sargolzaei M, Baes C, Cánovas A, Squires J, Miglior F. 2019. Genome-wide association analysis for β-hydroxybutyrate concentration in milk in Holstein dairy cattle. BMC Genet. 20(1):58.
Negussie E, Mehtia T, Mäntysaari P, Lovendahl P, Mäntysaari EA, Lidauer MH. 2019. Reliability of breeding values for feed intake and feed efficiency traits in dairy cattle: when dry matter intake records are sparse under different scenarios. J Dairy Sci. 102(8):7248–7262.
Olivieri BF, Mercadante MEZ, Cyrillo JNdSG, Branco RH, Bonilha SFM, de Albuquerque LG, Silva RMDo, Baldi F. 2016. Genomic regions associated with feed efficiency indicator traits in an experimental Nellore cattle population. PLOS One. 11(10):e0164390.
Onteru SK, Gorbach DM, Young JM, Garrick DJ, Dekkers JC, Rothschild MF. 2013. Whole genome association studies of residual feed intake and related traits in the pig. PLOS One. 8(6):e61756.
Pasam RK, Bansal U, Daetwyler HD, Forrest KL, Wong D, Petkowski J, Willey N, Randhawa M, Chhetri M, Miah H, et al. 2017. Detection and validation of genomic regions associated with resistance to rust diseases in a worldwide hexaploid wheat landrace collection using BayesR and mixed linear model approaches. Theor Appl Genet. 130(4): 777–793.
Prucz JE, Arias J, Bowman PJ, Davis SR, Macdonald KA, Waghorn GC, Wales WJ, Williams YJ, Spelman RJ, Hayes BJ. 2012. Accuracy of genomic predictions of residual feed intake and 250-day body weight in growing heifers using 625,000 single nucleotide polymorphism markers. J Dairy Sci. 95(4):2108–2119.
Pulina G, Tondo A, Danieli P P, Priml R, Crovotto GM, Fantini A, Macciotta NP P, Atzori AS. 2020. How to manage cows yielding 20,000 kg of milk: Technical challenges and environmental implications. Ital J Anim Sci. 19(1):865-879.
Purcell PJ, Law RA, Gordon AW, McGettrick SA, Ferris CP. 2016. Effect of concentrate feeding method on the performance of dairy cows in early to mid lactation. J Dairy Sci. 99(4):2811–2824.
Purfield DC, Evans RD, Berry DP. 2019. Reaffirmation of known major genes and the identification of novel candidate genes associated with carcass-related metrics based on whole genome sequence within a large multi-breed cattle population. BMC Genomics. 20(1):1–17.
Rainard P, Riollet C, Berthon P, Cunha P, Fromageau A, Rossignol C, Gilbert FB. 2008. The chemokine CXCL3 is responsible for the constitutive chemotactic activity of bovine milk for neutrophils. Mol Immunol. 45(15): 4020–4027.
Reverter A, Porto-Neto LR, Fortes MRS, Kasarapu P, De Cara MAR, Burrow HM, Lehnert SA. 2017. Genomic inbreeding depression for climatic adaptation of tropical beef cattle. J Anim Sci. 95(9):3809–3821.
Roberts SL, Lancaster PA, DeSilva U, Horn GW, Krehbiel CR. 2015. Coordinated gene expression between skeletal muscle and intramuscular adipose tissue in growing beef cattle. J Anim Sci. 93(9):4302–4311.
Romanzin A, Degano L, Vicario D, Spanghero M. 2021. Feeding efficiency and behaviors of Simmental bulls selected for high growth capacity: comparison of bulls with high vs. low residual feed intake. Livest Sci. 249: 104525.
Sarghale AJ, Shahrebabak MM, Shahrebabak HM, Javaremi AN, Saatchi M, Khansefid M, Miar Y. 2020. Genome-wide association studies for methane emission and ruminal volatile fatty acids using Holstein cattle sequence data. BMC Genet. 21(1):1–14.
Seabury CM, Oldeschulte DL, Saatchi M, Beever JE, Decker JE, Halley YA, Bhattacharriy EK, Molaei M, Freely HC, Hansen SL, et al. 2017. Genome-wide association study for feed efficiency and growth traits in U.S. beef cattle. BMC Genomics. 18(1):386.
Serão NV, González-Peña D, Beever JE, Faulkner DB, Southey BR, Rodríguez-Zas SL. 2013. Single nucleotide polymorphisms and haplotypes associated with feed efficiency in beef cattle. BMC Genet. 14:94.
Sharifi S, Pakdel A, Ebrahimi M, Reecy JM, Fazeli Farsani S, Ebrahimie E. 2018. Integration of machine learning and meta-analysis identifies the transcriptomic bio-signature of mastitis disease in cattle. PLOS One. 13(2):e0191227.
Silva AA, Silva DA, Silva FF, Costa CN, Silva HT, Lopes PS, Veronze R, Thompson G, Carvalheiro J. 2020. GWAS and gene networks for milk-related traits from test-day multiple lactations in Portuguese Holstein cattle. J Appl Genet. 61(3):465–476.
Taussat S, Boussaha M, Ramayo-Caldas Y, Martin P, Venot E, Cantalapiedra-Hijar G, Hoze C, Fritz S, Renand G. 2020. Gene networks for three feed efficiency criteria reveal shared and specific biological processes. Genet. Sel. Evol. 52(1):1–14.
Van Arendonk JM, Nieuwhof GJ, Vos H, Korver S. 1991. Genetic aspects of feed intake and efficiency in lactating dairy heifers. Livest Prod Sci. 29(4):263–275.
VanRaden PM. 2008. Efficient methods to compute genomic predictions. J Dairy Sci. 91(11):4414–4423.
Widdison S, Coffey TJ. 2011. Cattle and chemokines: evidence for species-specific evolution of the bovine chemokine system. Anim Genet. 42(4):341–353.
Xu F, Shan S, Sommerlad S, Seddon JM, Brenig B. 2021. A missense mutation in the KLF7 gene is a potential candidate variant for congenital deafness in Australian stumpy tail cattle dogs. Genes. 12(4):467.
Xue W, Wang W, Jin B, Zhang X, Xu X. 2016. Association of the ADRB3, FABP3, LPE, and LPL gene polymorphisms with pig intramuscular fat content and fatty acid composition. Czech J Anim Sci. 60(No. 2):60–66.
Yao C, Spurlock DM, Armentano LE, Page CD, Jr VandeHaar MJ, Bickhart DM, Weigel KA. 2013. Random Forests approach for identifying additive and epistatic single nucleotide polymorphisms associated with residual feed intake in dairy cattle. J Dairy Sci. 96(10):6716–6729.
Zhang F, Wang Y, Mukibi R, Chen L, Vinsky M, Plastow G, Basarab J, Stothard P, Li C. 2020. Genetic architecture of quantitative traits in beef cattle revealed by genome wide association studies of imputed whole genome sequence variants: I: feed efficiency and component traits. BMC Genomics. 21(1):36.
Zhang H, Shen LY, Xu ZC, Kramer LM, Yu JQ, Zhang XY, Na W, Yang LL, Cao ZP, Luan P, et al. 2020. Haplotype-based genome-wide association studies for carcass and growth traits in chicken. Poul Sci. 99(5):2349–2361.