Integrating a genome-wide association study with transcriptome analyses to identify candidate genes and pathways for feed conversion ratio in Yorkshire pigs

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Abstract

Background: Feed conversion ratio (FCR) is an important productive trait that largely affects profits in pig industry. Elucidating the genetic mechanisms underpinning the FCR potentially promote the efficiencies of improving FCR through artificial selection. In this study, we integrated a genome-wide association study (GWAS) with transcriptome analyses in different tissues in Yorkshire pigs (YY), aimed at identifying key genes and signaling pathways significantly associated with FCR.

Results: A total of 61 significant single nucleotide polymorphism (SNPs) were detected by GWAS in YY. All of these SNPs are located on porcine chromosome (SSC) 5 and the covered region was considered as a quantitative trait locus (QTL) region for FCR. Some genes that distributed around these significant SNPs were considered as the candidates for regulating FCR, including TPH2, FAR2, IRAK3, YARS2, GRIP1, FRS2, CNOT2 and TRHDE. According to the transcriptome analyses in hypothalamus, TPH2 exhibits abilities of regulating the intestinal motility by a serotonergic synapse and an oxytocin signaling pathway. In addition, GRIP1 is
involved in a glutamatergic and GABAergic signaling pathway, which regulates FCR through
affecting the appetite in pigs. Moreover, GRIP1, FRS2, CNOT2, TRHDE regulates the
metabolism in various tissues by a thyroid hormone signaling pathway.

Conclusions: Synthesizes results from GWAS and transcriptome analyses, TPH2, GRIP1, FRS2,
TRHDE, CNOT2 genes were considered as candidate genes for regulating FCR in Yorkshire pigs.
These findings help to improve the understandings of the genetic mechanism of FCR and
potentially optimize the design of breeding schemes.

Keywords: GWAS, Transcriptomics, Feed conversion ratio, Pigs
Improving feed conversion ratio (FCR) has become an imperative goal for the pig industry since it largely affects the economic profits [1, 2]. FCR is influenced by many factors, such as the level of metabolism, body composition and physical activities. Besides, genetic effect is also non-negligible for improving FCR [1, 3, 4]. FCR can be improved through artificial selection, but the progress is time-consuming and expensive [5]. Elucidating the genetic mechanisms underpinning FCR and identifying the significantly associated genes of FCR potentially enhance the efficiency of the improvement of FCR.

Genome-wide association analysis (GWAS) is an effective method to detect genetic variants and candidate genes associated with FCR, such as [6-8]. Overall, a large number of SNPs located on SSC 1, SSC 4, SSC 6, SSC 7 and SSC X have been identified significantly associated with FCR. Some QTL regions and candidate genes have been reported to be associated with FCR by using GWAS [9-12]. Therein, the marker WU_10.2_7_18377044 on SSC 7 have been reported explaining about 2.37% of phenotypic variance for residual feed intake (RFI), and DRGA0001676 on SSC 1 explained 3.22% and 5.46% of phenotypic variance for FCR and RFI, respectively [6]. Furthermore, QTL regions for the component trait of RFI were detected on SSC 1, 8, 9, 13 and 18 [8]. In addition, MC4R, XIRP2, TTC29, SOGA1, GRK5, PROX1, NMBR, KCTD16, ASGR1, PRKCQ, PITRM1 and TIAM1 have been reported as candidate genes for FCR in pigs by GWAS [9-12].

Transcriptome sequencing has also been comprehensively used to identify candidate genes and to unravel the molecular mechanisms for FCR. The pathways of hormonal regulation, notch signaling, and Wnt signaling in pituitary tissue have been reported to regulate FCR in pigs [13].
Also, VA metabolism, which can regulate fatty acid and steroid hormones metabolism, has been found to be associated with FCR in liver tissue of pig [14]. Moreover, in skeletal muscle tissue, genes involved in mitochondrial energy metabolism were down-regulated and genes involved in skeletal muscle differentiation and proliferation were up-regulated in skeletal muscle tissues of pigs with high FCR [15]. Gradient boosting machine learning for muscle transcriptomes indicated that FKBP5, MUM1, AKAP12, FYN, TMED3, PHKB, TGF, SOCS6, ILR4, and FRAS1 were related to FCR in pigs [16]. Transcriptomes in caecal and colonic mucosal tissues indicated energy and lipid metabolism can affect the FCR in pigs, and GUCA2A, GUCA2B, HSP70.2, NOS2, PCK1, SLCs, and CYPs were positively associated with FCR in pigs [17]. Although these studies have successfully identified some important signaling pathways and candidate genes of FCR, the molecular mechanisms of FCR are still remain to be clarified to a large extent. So far, to our knowledge, few studies have integrated results of GWAS and transcriptome analyses to identify the major genes and crucial signaling pathways of FCR in pigs. Thus, the objectives of our study were to identify QTLs and unravel the genetic architecture affecting FCR in Yorkshire pigs by performing both GWAS and transcriptome analyses in pig tissues that are related to the progress of FCR. This integrated analysis may help to enhance the power and efficiency of identifying candidate genes and key signaling pathways of FCR in Yorkshire pigs.

**Materials and Methods**

**Phenotypic recordings**

In this study, all the FCR (= feed intake/weight gain) were measured in Yorkshire pigs by a pig performance testing system in a national pig nucleus herd in the interval 30 to 100 kg. In total, 14
401 pigs had FCR recordings. All of the phenotypic recordings were measured between the year 2017 and 2020. Pedigrees can be traced back for ten generations. Totally, there are 19811 pigs existing in the pedigree.

**Genotypes**

The SNP markers were genotyped on 3672 YY pigs by using Illumina PorcineSNP60 Genotyping BeadChip (Vanraden, 1992). SNPs were mapped to pig chromosomes using the pig genome build 10.2 [18]. Quality controls were applied as follows: animals with call-rate smaller than 90% were first removed; SNPs with call-rate smaller than 90% were removed as well; SNPs with minor allele frequency smaller than 0.05 were filtered out; SNPs that deviated strongly from Hardy Weinberg equilibrium within breed (p < 10-7) were also excluded. After quality control, 31236 SNPs distributed over the 18 porcine autosomes were used for genome-wide association analysis.

**Statistic model for genomic prediction**

The single-step GBLUP (ssGBLUP) method was used to predict genomic breeding values (GEBVs) [19, 20]:

\[
y = Xb + Zu + e
\]  

(1)

where \( y \) contained phenotypic recordings for FCR; \( Xb \) indicated the fixed effects, including unit-year-month effect, sex effect and covariate for the starting weight; \( u \) was random additive effect and \( Z \) was the incidence matrix to relate the additive effects to the phenotypic recordings; \( e \) was a vector of residual effects. It was assumed that the random additive effects followed normal distribution, as: \( u \sim N(0, H \sigma_u^2) \), where \( H \) was the combined pedigree and genomic information
relationship matrix [19].

After estimating GEBVs, together with the pedigree information, de-regressed EBVs (DEBV) for all the involved animals were calculated as [21].

\[
\text{DEBV}_i = \mu + \sum_{j=1}^{k} Z_{ij}u_j + \epsilon_i
\]  

(2)

Where \( \text{DEBV}_i \) was the DEBV of animal \( i \) for the FCR, \( \mu \) was the overall mean, \( k \) was the total SNP markers number (31236), \( Z_{ij} \) was the allelic state at locus \( j \) in individual \( i \); \( u_j \) was the random effect of marker \( j \); and \( \epsilon_i \) was a random residual effect assumed to be normally distributed \( \epsilon_i \sim N(0, \sigma^2_e) \), where \( I \) was an identity matrix and \( \sigma^2_e \) was the residual variance [22-24].

**Genome-wide association studies**

The genome-wide association study was performed on 3672 genotyped pigs, by using MLMA (mixed linear model based association analysis) option of GCTA software [25]. All the SNPs were used for the association analysis. The mixed linear model was:

\[
y = 1\mu + xb + wg + e
\]  

(3)

where \( y \) was the vector of DEBVs for FCR in the genotyped Yorkshire pigs; \( \mu \) was the overall mean and \( 1 \) was a vector of ones; \( x \) was a vector of SNP genotypes, with entries 0, 1, 2 for genotypes AA, AB and BB, respectively; \( b \) was the fixed additive genetic effect of analyzed SNP; \( g \) was a vector of random polygenic effects and \( w \) was the incidence matrix relating the DEBVs to the corresponding random polygenic effects. It was assumed that \( g \) followed a normal distribution.
with mean of 0 and variance of $A\sigma^2_g$, where $A$ was the pedigree-based additive relationship matrix.

e was a vector of residual effects, following a normal distribution as $e \sim N (0, D\sigma^2_e)$, where $D$ was a diagonal matrix with elements $d_{ii} = (1 - r^2_{DEBV})/r^2_{DEBV}$ and $r^2_{DEBV}$ was the reliabilities for DEBVs. Significant test of SNP effects was implemented by a two-sided t-test. Bonferroni corrections were set as the genome-wide significant threshold ($-\log_{10}(0.05/\text{number of SNPs}) = 5.796$).

Detection of LD block and QTL analysis

Significant SNPs located within 1 Mb from each other were considered belonging to a same QTL region. Detection of LD block was performed in chromosomal regions where the identified significantly associated SNPs existed by the software Haplovie [26]. NCBI Remap was used to transfer the significant regions on SSC 5 aligned to the Sscrofa 10.2 genome assembly to that aligned to Sscrofa 11.1 genome assembly. Then, QTLs which are located in these significant regions were identified by being searched in a pig QTL database (pigQTLdb, https://www.animalgenome.org/cgi-bin/QTLdb/SS/index).

Candidate gene search and integrating analysis with transcriptome data

Genes that are located in the identified QTL region and 0.5 Mb flanking these loci were considered as candidate genes for regulating FCR [8, 27]. Then we used an omics knowledgebase, ISwine (http://iswine.iomics.pro), to search candidate genes based on genome, transcriptome, quantitative traits and annotation information [28]. Transcriptome analyses in different tissues (muscle, liver, fat, hypothalamus) collected from Yorkshire pigs with high or low performance of
FCR were implemented in previous studies in our lab [29]. Subsequently, the genes identified by ISwine and GWAS were integrated analyzed with transcriptome results. Database for Annotation, Visualization and Integrated Discovery software (DAVID bioinformatics resources: https://david.ncifcrf.gov/) was used for functional classification and pathway analysis for all the identified genes.

Results

Genome-wide association analyses for FCR

In total, 61 SNPs reached the significant thresholds of 5.796, which was calculated as the Bonferroni correction (=−log10(0.05/31326)) [30]. All the significantly associated SNPs (61 SNPs) are located on SSC 5. Among these SNPs, most of them (54 SNPs) are located within the region of 36.1-44.3 Mb on SSC 5, while 5 SNPs are located within the region of 47.1-47.8Mb and 2 SNPs are located within the region of 33.4–34.5Mb.

LD block, associated regions analysis and candidate genes identified for FCR

Several linkage disequilibrium (LD) blocks were detected in the regions where the 61 significantly associated SNPs located: 3 LD blocks were detected in the region of 33.4-34.5Mb on SSC 5; 3 LD blocks were detected in the region of 36.1- 44.3Mb on SSC 5 and 1 LD block was detected in the region of 47.1- 47.8Mb on SSC 5 (Figure 2). The region 33.4-34.5 Mb, 36.1- 44.3 Mb, 47.1- 47.8 Mb on SSC 5 maps on the Sscrofa 10.2 genome assembly was transfer to 30.2-31.3 Mb,
33.6-41.08 Mb, 43.8-44.5 Mb on SSC 5 aligned to the Sscrofa 11.1 genome assembly by NCBI Remap. Then, pigQTLdb [31] was used to identified QTLs in these regions, and the results showed these regions contained QTLs regulating the traits of days to 110 kg, feed intake, average daily gain, body weight, loin percentage, intramuscular fat content, average backfat thickness, etc. (Table S1). Feed intake and growth traits are tightly related to the performance FCR. Thus, these regions were also considered as crucial QTL regions associated with FCR.

All the detailed information of the significantly associated SNPs identified by GWAS and the putative candidate genes in this QTL region is shown in Table S2. Among the identified 61 significantly associated SNPs, 26 SNPs are located within some different genes. These significant SNPs together with their corresponding genes are shown in Table 1. Some other genes located in the 0.5 Mb genome region flanking the significantly associated SNPs were also considered as candidate genes, including revealed fibroblast growth factor receptor substrate 2 (FRS2), tryptophan hydroxylase 2 (TPH2), thyrotropin releasing hormone degrading enzyme (TRHDE), GLI pathogenesis related 1 (GLIPR1) and fatty acyl-CoA reductase 2 (FAR2) etc. ISwine platform [28] was also used to identify candidate genes for FCR in pigs. All the candidate genes identified by ISwine platform are shown in Table S3. Based on the results from ISwine, TRHDE, TPH2, FAR2, FRS2, GLIPR1 genes were confirmed as candidate genes for regulating FCR in Yorkshire pigs.

**Integrated analysis between GWAS and transcriptome analyses**

To clarify the genetic mechanisms that involved in the regulation of FCR in pigs, we integrated the GWAS results with a previously published transcriptome data of FCR, by using DAVID [32].
The discovered signaling pathways and possible major genes are showed in Figure 3. It showed that a mutation in TPH2 gene may influence the expression of neurotransmitter serotonin (5-HT), which mediates colonic motility by the secretion of hypothalamic oxytocin (Figure 3a). In addition, a mutation in GRIP1 gene may influence the aggregation of GABA and glutamate, which mediates appetite of pigs (Figure 3c). Notably, a thyroid hormone signaling pathway, which is regulated by GRIP1, FRS2, CNOT2, TRHDE genes, was significantly differently expressed in pigs with high or low FCR. The thyroid hormone signaling pathway participates in the regulation of metabolism in various tissues (Figure 3b).

Discussion

QTLs, LD blocks and candidate genes for FCR

Feed efficiency (FE) is an important economic trait that largely affects the economic profit of breeding industry. Identification of major genes regulating FE may help to enhance the efficiency of improving FE through technology of molecular breeding. FE is a complex trait that is regulated by many genes located in different chromosomes. So far, only a few candidate genes have been identified due to the difficulty of collecting a large number of FCR recordings and ratio trait is usually hard to be analyzed accurately. Some QTL regions associated with feed efficiency have been identified in previous studies, for example, 27-33 Mb on SSC 1, 63.8-64.0 Mb on SSC 4, 32.4-38.9 Mb and 77.8-84.2 Mb on SSC 16, 26-35 Mb on SSC 18 [8, 27, 33]; the genes CTSK, IGF2BP, MC4R, MAP3K5, DSCAM were detected as the candidate genes for feed efficiency [33, 34]. These genes mainly related to lipid metabolic process, inositol phosphate metabolism and insulin signaling pathways. In the
current study, we implemented a genome-wide association analysis for FCR in a large Yorkshire population. Our analyses identified a series of novel significant SNPs located in the 33.4-34.5 Mb, 36.1- 44.3 Mb, 47.1- 47.8 Mb on SSC 5. LD analysis showed these regions are highly linked, and many QTLs related to feed intake and growth traits were located in these regions. Logically, these regions were considered as candidate QTL regions for FCR. Genes located within 1Mb of the significantly associated SNPs, including Fatty acyl CoA reductase 2 (FAR2), Interleukin-1 receptor-associated kinase-3 (IRAK3), and tyrosyl-tRNA synthetase 2 (YARS2), were inferred as candidate genes regulating FCR in our study.

FAR2 gene spanned from 44.38Mb to 44.55Mb on SSC5. It is a key gene for fatty acid β-oxidation, acetyl-CoA translocation, peroxisome biogenesis, and the glyoxylate cycle [35]. Moreover, FAR2 were associated with insulin resistance [36]. Previous studies reported that lipid metabolism can explain the variation of FCR [14, 37, 38]. Therefore, the gene FAR2 might be a candidate gene for FCR.

IRAK3 belongs to serine-threonine kinases and it is negatively correlated with mitochondrial oxidative stress marker SOD2. It has been reported that high IRAK3 and low SOD2 cause weight loss [39, 40]. Previous studies reported that decreased IRAK3 was associated with increased mitochondrial reactive oxygen species (ROS) [41] and some other studies reported that ROS can decrease muscle mass by regulating mitochondrial biogenesis and the expression of antioxidant gene [42, 43]. Mitochondrial energy metabolism is a potential factor affecting the Feed conversion ratio in pigs [15]. Therefore, IRAK3 is worthy to be further functionally investigated.

YARS2 is a key gene binds tyrosine to the homologous mt-tRNA for the synthesis of
mitochondrial proteins. The mutations of YARS2 can lead to mitochondrial respiratory chain complex deficiencies and are related to mitochondrial myopathy [44, 45]. YARS2 has not been functionally characterized in pigs. However, since its function involves mitochondrial protein synthesis and mitochondrial respiratory, it might be an important candidate gene for FCR in pigs.

**GRIP1 control appetite through glutamatergic and GABAergic signaling**

In this study, we integrated GWAS results with transcriptome analyses, aiming at identifying candidate genes and biological pathways of FCR in pigs. The performances of feed intake have been found significantly different in FCR divergent selection pigs, meanwhile feed intake is a major physiological process associated with variations of FCR [46-48]. GABA (γ-amino-butyric acid) and glutamate, which express in hypothalamic neurons, can promote feeding and weight gain, while GRIP1 can interact with the C termini of AMPA receptors and clustered at both glutamatergic and GABAergic synapses [49-51]. In addition, the genes associated with GABAergic synapse (GNG13, GABRA5, GABRE, GABRQ, GAD2, HAP1, PRKCG) and Glutamatergic synapse (GNG13, GRM4, KCNJ3, PRKCG, SLC17A6, SLC17A7) were detected differently expressing in hypothalamic tissue in pigs with high or low performance of FCR [52]. Therefore, GRIP1 may control appetite through glutamatergic (Figure 4a) and GABAergic signaling pathway (Figure 4b). Moreover, two informative SNPs in GRIP1 were identified significantly associated with backfat thickness in pigs [53]. So, GRIP1 was an important candidate gene for FCR in pigs.

**TPH2 affects 5-HT secretion, thereby mediates intestinal motility through hypothalamus oxytocin signaling pathway**
Brain-gut interactions may be an important factor for Feed conversion ratio in pigs[54]. The central neurotransmitter serotonin (5-hydroxytryptamine, 5-HT), produced by tryptophan hydroxylase 2 (Tph2), mediates colonic motility by regulating oxytocin (OT) synthesis in the hypothalamus [55, 56]. In addition, knockout TPH2 in mice showed depleted 5-HT in brain and the mice showed an increased food consumption, modest impairment of sleep and respiration accompanied [57]. Therefore, TPH2 can regulate appetite and intestinal motility by affecting the secretion of 5-HT. In our results, a significant SNP (SNPID) has been found locating in the TPH2 gene. Moreover, transcriptome sequencing in hypothalamic of pigs with extremely high or low feed efficient exhibited that the genes related to serotonergic synapse (GNG13, ALOX5, KCNN2, KCNJ3, PTGS1, PRKCG) and oxytocin signaling pathway (CACNB4, CAMKK2, NPR1, OXT, KCNJ3, PRKCG) were differentially expressed [52]. RNA-seq in caecal and colonic mucosa exhibited the genes NOS2, related to gastrointestinal peristalsis, was a candidate gene for FCR [17]. Therefore, the SNPs within TPH2 may change the expression of this gene, and thereby affecting the secretion of 5-HT. Sequentially 5-HT regulates intestinal motility through hypothalamus oxytocin signaling pathway.

**GRIP1, FRS2, CNOT2, TRHDE affects metabolic processes**

Thyroid hormone (TH), regulated by the thyrotropin releasing hormone (TRH) and thyroid stimulating hormone (TSH), is involved in regulating many metabolic processes essential for growth and development, including basal metabolic rate, facultative thermogenesis, skeletal muscle growth, regulation of body weight, and lipid metabolism [58-60]. Thyroid hormone receptors (TR) mediates the biological effects of thyroid hormone (T3) [61]. In our result, many
candidate genes participated in regulating TH signaling, including GRIP1, FRS2, CNOT2, TRHDE and so on. Among them, GRIP1 acts as a coactivator for TR, strengthening the combination of TR and TH [62, 63]. FRS2 involved in FGF21-AMPK signaling and it can be induced to express to accelerate the energy metabolism by the thyroid hormone [64]. CNOT2 is an important regulator for energy metabolism, cellular stress and fatty acid metabolism in the skeletal muscles. The heterozygous intragenic deletion of CNOT2 displayed disordered phenotypes of learning disability, developmental delay, and hypothyroidism [65, 66]. TRHDE is an extracellular peptidase that specifically degrades the TRH to regulate appetite and metabolism [67, 68]. SNP association analysis in a New Urumqi Sheep population showed that TRHDE gene significantly associated with body weight [69]. Moreover, transcriptome sequencing in hypothalamic of pigs with high or low FCR exhibited that the genes involved in thyroid hormone signaling pathway (TRH, PIK3CG, PLCD4, PRKCG) and Autoimmune thyroid disease (SLA-DMB, SLA-DMA) were different expression [52]. Therefore, different FCR pigs were mediated by thyroid signaling pathway in hypothalamic, thus showing different phenotypes and gene differential expression in muscle, fat, liver and others tissues.

It has been reported that TH stimulated oxidation to maintain ATP synthesis by increasing proton leakage from the mitochondrial inner membrane in skeletal muscle and TH regulated the contractile function, regeneration, and transport of skeletal muscle [70-72]. Transcriptome analysis in skeletal muscle exhibited that the mitochondrial energy metabolism and skeletal muscle differentiation and proliferation were associated with FCR [15]. TH also targeted at the metabolic activities of lipid in fat and liver, such as cholesterol synthesis, cholesterol efflux, bile acid synthesis, fatty acid metabolism and hepatic steatosis [73-77]. Transcriptome analysis in adipose
tissue indicated that lipid metabolism affects the FCR in pigs [37]. Liver is an important tissue for
maintain the homeostasis of metabolic processes. Transcriptome analysis in liver revealed that
vitamin A, fatty acid, and steroid hormone metabolism were related to FCR [14].

Conclusions

This study detected a novel QTL region on SSC 5 that is significantly associated with feed
conversion ratio in Yorkshire pigs. An integrative analysis of the GWAS results and transcriptome
results in different tissues has been used to identify candidate genes and signaling pathways that
play a decisive role in feed conversion ratio in pigs. Important genomic mutation that results in
changing the RNA expression of hypothalamus, muscle, fat, liver, caecal and colonic mucosa in
pigs with high or low FCR was elaborated by combining results from genomic and transcriptome
analyses in different tissues. We concluded that through controlling feed intake and thyroid
hormone signaling pathway in hypothalamic, GRIP1, TPH2, FRS2, CNOT2, TRHDE genes
regulate metabolism in different pig tissues, resulting in a variation of FCR. These findings shed
new light on the importance of the genomic and transcriptome interactions in regulating feed
conversion ratio in pigs and offer a better understanding of the molecular mechanisms regulating
feed conversion ratio in pigs.

Abbreviations

CNOT2: CCR4-NOT transcription complex subunit 2; DEBV: de-regressed estimated breeding values; FAR2:
fatty acyl-CoA reductase 2; FCR: Feed conversion ratio; FRS2: fibroblast growth factor receptor substrate 2;
GEBVs: genomic estimated breeding values; GRIP1: GLI pathogenesis related 1; GWAS: genome-wide
association study; IRAK3: interleukin 1 receptor associated kinase 3; LD block: linkage disequilibrium block;
MLMA: mixed linear model based association analysis; pigQTLdb: pig QTL database; QTL: quantitative trait
locus; TIAM1: SNP: single nucleotide polymorphism; ssGBLUP: single-step genotype best linear unbiased
prediction; TPH2: tryptophan hydroxylase 2; TRHDE: thyrotropin releasing hormone degrading enzyme; YARS2:
YY: Yorkshire pigs;
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Authors' contributions

Tao xiang, Shuhong Zhao and Xinyun Li conceived and designed the experiments; Yuanxin Miao, Quanshun Mei and Chuanke Fu analyzed the data; Yuanxin Miao and Mingxing Liao contributed materials/analysis tools; Yuanxin Miao, Tao Xiang, Shuhong Zhao wrote the manuscript and all authors contributed to finalizing the writing.

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Availability of data and materials

The datasets analyzed during the current study are available from the corresponding author upon request.

Ethics approval and consent to participate

Not applicable.

Consent for publication

Not applicable.

Competing interests

The authors declare no conflict of interest.

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**Figures**

**Figure 1:** Manhattan plot of genome-wide associated analysis studies for FCR. The solid line indicate Bonferroni corrected p-value=5.796.
Figure 2: Linkage disequilibrium block on chromosome 5. Markers in blocks shown in bold.

Legends: (a) Linkage disequilibrium block detected in the regions from 33.4 to 34.5 Mb on SSC5, (b) Linkage disequilibrium block detected in the regions from 36.1 to 44.3 Mb on SSC5, (c) Linkage disequilibrium block detected in the regions from 47.1 to 47.8 Mb on SSC5. SNPs in red boxes are significantly associated with FCR.
Figure 3: Theoretical models of functional actions of candidate genes in modulating feed
conversion ratio. (a) TPH2 regulates the intestinal motility by serotonergic synapse and oxytocin signaling pathway in hypothalamus. TPH2 produces 5-HT and 5-HT transmits signals to oxytocin neurons through serotonergic synapse, and subsequently regulates intestinal peristalsis under the action of the oxytocin signaling pathway. (b) GRIP1, FRS2, CNOT2, TRHDE genes regulate the metabolism in various tissues by a thyroid hormone signaling pathway. GRIP1, FRS2, CNOT2 and TRHDE regulate the thyroid signaling pathway in hypothalamus first and subsequently, the thyroid signaling pathway participate in regulating the metabolism in skeletal muscle, liver and fat. (c) GRIP1 regulates the appetite by a glutamatergic and GABAergic signaling.
Figure 4: GRIP1 regulates the appetite by a glutamatergic synapse (a) and GABAergic synapse (b).
Figure 5: 5-HT, produced by TPH2, regulates the serotonergic synapse pathway (a) and oxytocin signaling pathway (b) in hypothalamus.
Table 1 Summary information of within genes significant SNPs for FCR trait

| SNP ID    | bp (SSC10.2) | bp (SSC11.1) | Pvalue     | Genes |
|-----------|--------------|--------------|------------|-------|
| rs80841312| 36496185     | 33897913     | 4.39E-07   | CCT2  |
| rs80786392| 36510853     | 33912700     | 4.51E-07   | BEST3\ CNT2 |
| rs80837106| 36589679     | 33991092     | 4.51E-07   | CCT2  |
| rs80845463| 36621274     | 34022700     | 4.51E-07   | CCT2  |
| rs81383707| 36721314     | 34122773     | 4.54E-07   | MYRFL |
| rs80964888| 36532511     | 33934311     | 4.72E-07   | BEST3\ CNT2 |
| rs332237334| 36353885   | 33842149     | 4.79E-07   | FRS2  |
| rs81344478| 36357722     | 33838344     | 4.79E-07   | FRS2  |
| rs80850598| 37318776     | 34747588     | 4.93E-07   | PTPRB |
| rs81287625| 36826851     | 34177721     | 5.25E-07   | MYRFL |
| rs345043801| 36469745    | 33871482     | 6.03E-07   | CCT2  |
| rs80785563| 36544839     | 33946621     | 6.03E-07   | BEST3\ CNT2 |
| rs80989707| 36568996     | 33970407     | 6.35E-07   | CCT2  |
| rs339913443| 38629120   | 35929672     | 6.61E-07   | TPH2  |
| rs80835055| 36838800     | 34189654     | 7.00E-07   | MYRFL |
| rs81000718| 37249647     | 34677764     | 7.01E-07   | PTPRB |
| rs80892229| 37369531     | 34769398     | 7.44E-07   | PTPRB |
| rs323754097| 39138147   | 36346640     | 9.75E-07   | TRHDE |
| rs81383732| 38337110     | 35634440     | 1.01E-06   | ZFC3H1 |
| rs          | Marker1 | Marker2 | p-value   | Candidate Gene(s)         |
|-------------|---------|---------|-----------|---------------------------|
| rs80811321  | 34095144| 30820701| 1.26E-06  | GRIP1                     |
| rs8132542   | 47441081| 44096325| 1.37E-06  | TMTC1                     |
| rs81212454  | 42358084| 38794710| 1.46E-06  | GLIPR1, KRR1              |
| rs8138391   | 42378400| 38815027| 1.46E-06  | GLIPR1, KRR1              |
| rs81331039  | 47398882| 44127767| 1.49E-06  | TMTC1                     |
| rs81331835  | 47404818| 44121830| 1.49E-06  | TMTC1                     |
| rs81383984  | 47782626| 44464360| 1.58E-06  | FAR2                      |

Additional Files

Additional file 1: Table S1. Description of quantitative traits loci (QTL) regions for the significant regions associated with FCR.

Additional file 2: Table S2. Summary information of significant SNPs and candidate genes for FCR trait.

Additional file 3: Table S3. Candidate genes for FCR in pigs indentified by ISwine website.