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GENOME-WIDE ASSOCIATION STUDY FOR GROWTH AND FEED EFFICIENCY TRAITS IN RABBITS

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Abstract: Feed efficiency is a major production trait in animal genetic breeding schemes. To further investigate the genetic control of feed efficiency in rabbits, we performed a genome-wide association study (GWAS) for growth and feed efficiency on 679 rabbits genotyped with the Affimetrix Axiom Rabbit 200K Genotyping Array. After quality control, 127 847 single-nucleotide polymorphisms (SNP) were retained for association analyses. The GWAS were performed using GEMMA software, applying a mixed univariate animal model with a linear regression on each SNP allele. The traits analysed were weight at weaning and at 63 days of age, average daily gain, total individual feed intake, feed conversion ratio and residual feed intake. No significant SNP was found for growth traits or feed intake. Fifteen genome-wide significant SNPs were detected for feed conversion ratio on OCU7, spanning from 124.8 Mbp to 126.3 Mbp, plus two isolated SNP on OCU2 (77.3 Mbp) and OCU8 (16.5 Mbp). For residual feed intake, a region on OCU18 (46.1-53.0 Mbp) was detected, which contained a putative functional candidate gene, *GOT1*.

Key Words: feed efficiency, SNP, GWAS, genetics, candidate genes, rabbits.

INTRODUCTION

Improvement of feed efficiency is essential to increase the competitiveness of the rabbit industry but also to reduce animal excretion, and consequently decrease the environmental impact of production (Gidenne *et al.*, 2017a). Drouilhet *et al.* (2013, 2015) performed a selection to lower residual feed intake (RFI) in rabbits. Heritability of RFI estimated by the authors was moderate (0.16±0.05) (Drouilhet *et al.*, 2013). Accurately recording individual feed intake is costly and time consuming, and great efforts are made in other species to facilitate the improvement of feed efficiency by identifying genomic markers associated with this trait. Such approaches, including linkage analyses, genome-wide association studies (GWAS) and candidate gene association studies, have been performed to unravel the genetic background behind complex traits such as feed efficiency in pigs (Onteru *et al.*, 2013; Ding *et al.*, 2018; Delpuech *et al.*, 2021). In rabbits, following a first study for carcass traits (Sternstein *et al.*, 2015), association studies arose later, with the recent availability of the Axiom Rabbit 200K Genotyping Array, and first results are now available in various populations and traits, such as growth curve parameters (Liao *et al.*,2021), growth and carcass traits (Yang *et al.*, 2020), litter size (Sosa-Madrid *et al.*, 2020) and feed efficiency (Sánchez *et al.*, 2020). In this study, after estimating genetic parameters to quantify the genetic basis of the traits in the design, GWAS was performed on feed efficiency and growth traits in rabbits to identify genetic variants associated with these traits, and candidate genes were searched for.

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MATERIAL AND METHODS

Ethics statement

This study was carried out in accordance with the national regulations for animal care and use of animals in agriculture, at the INRAE farm Pôle d'Expérimentation Cunicole Toulousain (Castanet-Tolosan, France). It was reviewed and approved by the Animal Experimentation Ethics Committee n°115 (agreement number APAFiS #18 416), on behalf of the French Ministry for Higher Education, Research and Innovation.

Animals and phenotypes

The experimental rabbit population was issued from the paternal INRA 1001 line (Larzul and De Rochambeau, 2005). Two related genetic lines were used in this design: the G10 line, selected for 10 generations for decreased RFI (Drouilhet *et al.*, 2013, 2015), and the G0 control line, produced from offspring of frozen embryos of the ancestor population of the selected line. The 296 G10 were produced by mating 12 bucks with 50 does and the 292 G0 rabbits were produced by mating 10 bucks and 51 does in the same 3 batches, with a 42 d interval between batches. In each batch, half of the kits were reared by G0 does and the second half were reared by G10 does. Litters were made up by mixing 5 to 7 kits, each from different sire families of a given line. Does adopted kits alternatively from one line and from the other line in successive batches. At weaning (32 d), kits were placed in individual cages. From weaning to slaughtering, rabbits had free access to water and *ad libitum* access to a diet with commercial pellets. Pellets were composed of 14.4% crude protein, 27.9% acid detergent fibre, 9.9% acid detergent lignin, 8.8% crude ash, phosphorus 5.31 g/kg, zinc 100 mg/kg and copper 23.8 mg/kg. More details about the experiment can be found in Garreau *et al.* (2019).

Animals were weighed at weaning (BW32) and at 63 d of age (BW63). Total individual feed intake (FI) was recorded. Average daily gain (ADG) was obtained by dividing the body weight gain during the test by the number of days of the growing period (31 d). Feed conversion ratio (FCR) was calculated as total individual feed intake divided by the body weight gain. The RFI was computed as the residual of the multiple linear regression of total individual feed intake on average metabolic body weight (average body weight between weaning and end of the test to the power 0.75) to account for maintenance requirements, and ADG to account for production requirements (REG procedure; SAS software), as in Drouilhet *et al.* (2015).

Genotyping and genotype quality control

Ear biopsies were sampled at 63 d of age. The DNA was extracted from ear biopsies of 711 animals (588 kits and their 123 parents), following a salt-based DNA extraction protocol. Six hundred and ninety six animals were genotyped using the Affimetrix Axiom Rabbit 200K Genotyping Array (Santa Clara, CA, USA), containing 199 692 single-nucleotide polymorphisms (SNP), at the Centro Nacional de Genotipado (CeGen) platform (Santiago de Compostela, Spain). The order and position of the SNPs on the genome were based on the Rabbit OryCun2.0 assembly released by the Broad Institute of MIT and Harvard (Carneiro *et al.*, 2014). The 11 mitochondrial SNPs were discarded from the marker set, as well as 6267 and 7 SNPs located on sexual chromosomes X and Y, respectively. The QCF90 software (Masuda *et al.*, 2019) was used for the quality control. Three successive steps are run. The first step disqualifies markers based on call rate, MAF and number of autosomal heterozygotes, leading to new allele frequency counts. In the second step, animals are examined, signalling those presenting a call rate below threshold and/or Mendelian conflicts. The final and third step is based on the estimation of gene content heritability and allows us to discard markers with insufficient technical properties. Two rounds were carried out. First, with a threshold of 0.05 for minor allele frequency (MAF) and 0.90 for call rates, and second with a threshold of 0.95 for marker call rate, leading to a total of 686 animals (568 tested progeny) and 128 226 remaining SNPs (i.e. an average of 1 SNP every 20 kb) for further analyses.

Statistical analyses

The phenotypes of the 568 kits remaining after quality control were analysed to test systematic effects using the GLM procedure (SAS Inst., Inc., Cary, NC). The fixed effects tested for each trait were: sex (2 levels), batch (3 levels),

Table 1: Significance[1] of the fixed effects in linear models for growth and feed efficiency traits.

	BW32	BW63	ADG	FI	FCR	RFI
Sex	ns	**	**	*	ns	ns
Batch	***	***	**	***	***	***
Dam parity	ns	ns	ns	ns	**	*
Litter size at birth	***	***	**	***	***	***
Litter size at weaning	***	***	ns	***	***	ns

BW32: body weight at 32 d; BW63: body weight at 63 d; ADG: average daily gain; FI: total feed intake; FCR: feed conversion ratio; RFI: residual feed intake. [1]Significance levels from linear models including all effects.
*P<0.05; **P<0.01; ***P<0.001.

dam parity (4 levels), litter size at birth (4 levels:1 to 5, 6-7, 7-8, 9 and more), litter size at weaning (4 levels: 1 to 4, 5, 6, 7 and more). The fixed effects were considered significant when P value ≤0.05, and were included in the final model (Table 1).

Estimation of genetic parameters

For the six traits of interest, heritabilities were computed with restricted maximum likelihood (REML) using the following univariate mixed model: $y=Xb+Zu+\epsilon$, were b and u are the vectors of estimated fixed and polygenic effects respectively and ϵ is the vector of errors. Then y, a vector of size equal to 586, represents the phenotypes, while Z is the incidence matrix comprising indicators for the 1447 animals in the pedigree used to build the relationship matrix (*i.e.* up to the start of the above-mentioned selection for decreased RFI, thus encompassing common ancestors to the G0 and G10 populations). The blupf90+ software (Mizstal *et al*, 2014) was used to estimate variances, using genotype data in a ssGBLUP design (Mizstal *et al*, 2009), where the relationship matrix combined both pedigree and genomic information.

Genome-wide association studies

The GWAS were performed using GEMMA version 0.94.1 (Zhou and Stevens, 2012). For each trait, SNP effect a was successively tested at each position with the following animal mixed model: $y=Xb+xa+u+\epsilon$ with $u\sim N_n(0,K\sigma^2_u)$ and $\epsilon\sim N_n(0,I_n\sigma^2_\epsilon)$.

Here, $N_n(\mu,V)$ stands for a n-vector of Gaussian deviates of mean μ and variance V, y is the vector of phenotypes, X is the incidence matrix of fixed effects and b stands for the vector of these effects, a is the marker effect and x is the vector of marker genotypes, while u is the vector of random polygenic effect and ϵ is the vector of errors. Residual effects are assumed to be independent. Additive genetic effects were structured with K, the centred relatedness matrix computed from the genotypes and allele frequencies (VanRaden, 2008). The aim of using the relationship matrix is to control the stratification and relatedness in the experimental population.

Significance was assessed for each tested SNP based on the P values of the Wald test. To account for multiple testing, the significance threshold of the SNP P values was corrected via a Bonferroni adjustment thanks to the SimpleM software (Gao *et al.*, 2008, 2010). A principal component analysis is applied to the correlation matrix between SNP genotypes. The number of independent tests is assumed to be equal to the number of principal components retained to explain 99.5% of variance. The number of independent tests was first calculated for each of the 21 autosomes separately, and then summed to obtain the number of independent tests of the analysis. The total number of independent tests was 3804 for the 128 226 retained SNPs. Therefore, the genome-wide significance threshold for -log10(P values) was equal to 4.83.

Each set of SNPs with –log10(P values) above the threshold evidenced a region which could be characterised by the number of SNPs, their positions, and the proportion of variance explained by the leading SNP (i.e. the SNP exhibiting the largest score). The variance explained by the leading SNP is $V_{\widehat{SNP}} = 2\times p\times(1-p)\times a^2$, where, as above, a is the marker effect while p is the allele frequency.

Table 2: Heritability estimates and standard errors for growth and feed efficiency traits.

Trait	Heritability estimate	Standard error
BW32	0.14	0.06
BW63	0.24	0.07
ADG	0.33	0.07
FI	0.40	0.07
FCR	0.45	0.07
RFI	0.48	0.07

BW32: body weight at 32 d, BW63: body weight at 63 d, ADG: average daily gain, FI: total feed intake, FCR: feed conversion ratio, RFI: residual feed intake.

RESULTS AND DISCUSSION

Heritability estimates

Heritability estimates ranged between 0.14±0.06 and 0.33±0.07 for growth traits and between 0.40±0.07 and 0.47±0.06 for feed intake and efficiency traits (Table 2). These estimates were higher than those reported by Drouilhet *et al.* (2013) for the same traits from data recorded during the first 6 generations of selection in the same rabbit experimental line selected for RFI. In other rabbit lines under ad libitum feeding, heritability estimates of ADG ranged from 0.11±0.02 (Piles and Blasco, 2003) to 0.41±0.13 (Larzul and De Rochambeau, 2005). Lower heritabilities were also reported for FCR in the literature: 0.25±0.12 (line R; Piles *et al.*, 2004) and 0.31±0.10 (line C; Piles *et al.*, 2004). The high values of heritability estimated in our study for feed efficiency traits can be explained by the specific composition of our experimental population, half composed of rabbits selected for RFI and the other half of non-selected rabbits, thus gathering two connected but genetically different populations.

GWAS results

No significant SNP was found associated with growth traits and FI. Seventeen and 111 genome-wide significant SNPs were detected for FCR (Figure 1) and RFI (Figure 2), respectively (Table 3). For FCR, the most significant peak was located on chromosome 7, from 124.8 to 126.3 Mbp, with a total of 15 significant SNPs, explaining 4.53% of the phenotypic variance. One significant SNP was also located on chromosome 8 (16.5 Mbp) and another one on chromosome 2 (77.3 Mbp), but they were isolated. Based on the genome assembly, no functional candidate gene could be identified in these regions. The 111 significant SNPs for RFI were located on chromosome 18, covering a region from 46.1 to 53.0 Mbp (4.36% of the phenotypic variance). For both traits, the QQplots showed no deviation of the test statistics from what was expected, validating the control of the population structure in our analyses.

Despite the limited annotation of the rabbit genome, a putative functional candidate gene, *GOT1* (47.39-47.42 Mbp), was identified in this region. Glutamic-oxaloacetic transaminase is a pyridoxal phosphate-dependent enzyme that exists in cytoplasmic mitochondrial forms. *GOT1* plays a role in amino acid metabolism and in urea and tricarboxylic acid cycles (Mavrides and Christen, 1978). A significant positive correlation between RFI and faecal N was described by Aggrey *et al.* (2014) in broilers: the birds in the LRFI population attained greater feed

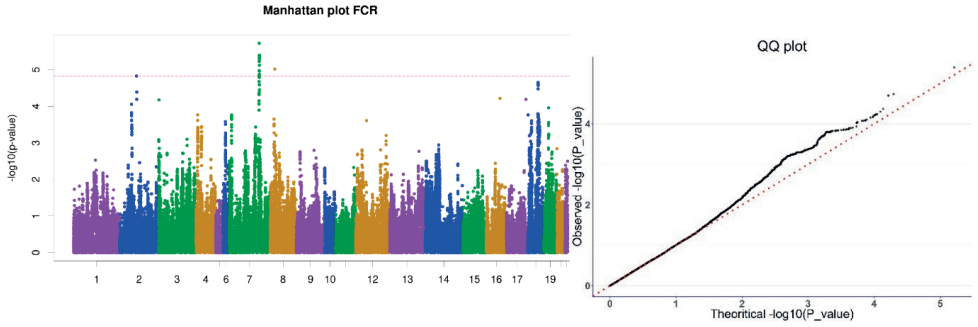

Figure 1: Manhattan plot (left) and Quantile-Quantile (QQ, right) plot for feed conversion ratio (FCR). Dashed line corresponds to the 5% genome-wide theshold. The dotted line on the QQ plot corresponds to the y=x line.

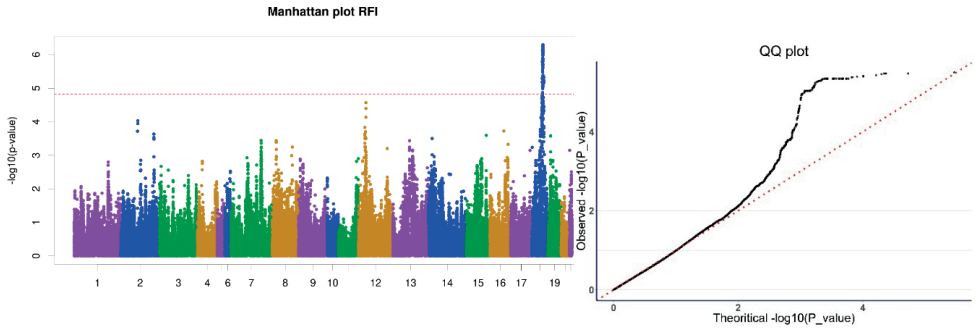

Figure 2: Manhattan plot and Quantile-Quantile (QQ) plot for residual feed intake (RFI). Dashed line corresponds to the 5% genome-wide theshold. The dotted line on the QQ plot corresponds to the y=x line.

efficiency by having lower FI, increasing their protein retention and, consequently, reducing faecal N. The same authors reported different gene expression levels of *GOT1* between two broiler lines divergently selected for RFI. *GOT1* was downregulated in four tissues (duodenum, muscle, liver and kidney) of the low RFI line. Mukiibi *et al.* (2018) also found differential expression of *GOT*1 between six extremely high and six extremely low RFI steers from three beef breed populations. The role of this gene in the metabolism of amino acids and urea is fully consistent with the results obtained from the comparison of the two lines that compose our experimental population (Gidenne *et al.*, 2017b): the N balance was improved in the G10 selected line compared to the G0 non-selected line (+5%), leading to a reduced N output either through the faeces (meanly -6 g/d compared to G0) or the urine (–0.07 g/d), and to an improved N retention ratio (+3% compared to G0).

In rabbits, very few QTL have been described in the literature. Sánchez *et al.* (2020) revealed a total of 189 SNPs significantly associated with ADG and feed efficiency traits, in 17 chromosomal regions but not on the chromosomes 7 or 18 revealed by our study. In 12 of the regions identified by these authors, 20 candidate genes were proposed to explain the variation of the analysed traits, including genes such as *FTO*, *NDUFAF6* and *CEBPA,* previously reported as associated with growth and feed efficiency traits in monogastric species. A total of 28, 81 and 10 significant SNPs were identified by Yang *et al.* (2020) for growth, carcass and meat quality traits, respectively, but the QTLs were located on different chromosomes than those identified in our study. Additionally, 16, 71 and 9 candidate genes within 100 kb upstream or downstream of these SNPs were proposed by the authors. Several candidate genes have been proposed in other studies for body weight at different ages (Zhang *et al.*, 2013; Helal *et al.*, 2019, 2021; Yang *et al.*, 2019) and meat quality (Zhang *et al.*, 2013; El-Sabrout *et al.*, 2018; Helal *et al.*, 2019, 2021; Yang *et al.*, 2019). Growth hormone genes (*GH, GHR*), insulin-like growth factor 2 gene (*IGF2*) and myostatin gene (*MSTN*) were the most frequent genes associated with growth and meat quality, but they were not in the vicinity of the regions detected in the present study.

Table 3: Characteristics of the evidenced regions for a putative quantitative trait locus (QTL) influencing feed conversion ratio (FCR) and residual feed inatke (RFI).

Trait	FCR	FCR	FCR	RFI
Chromosome	2	7	8	18
Number of single-nucleotide polymorphisms (SNP)	1	15	1	111
Position min (Mbp)	77.3	124.8	16.5	46.1
Position max (Mbp)	77.3	126.3	16.5	53.0
Position of leading SNP	77.3	124.9	16.5	48.3
-Log_{10}Pval of leading SNP	4.83	5.73	5.02	6.30
Percentage of variance explained by the leading SNP	2.73%	4.53%	3.05%	4.36%

CONCLUSIONS

A genome association study was performed in an experimental population that comprised rabbits selected for RFI and non-selected rabbits proportionally. One significant region was detected for feed conversion ratio and one for residual feed intake, covering about 1.5Mbp and 6.9 Mbp, respectively. On chromosome 18, we identified the putative candidate gene *GOT1* in the region associated with residual feed intake. The role of this gene in the metabolism of amino acids and urea is fully consistent with the improved N balance and the reduced N output observed in the G10 selected line, compared to the G0 non-selected line, as mentioned in a previous publication. Further functional research is needed to validate this gene.

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