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

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3 **GENOME WIDE ASSOCIATION STUDY FOR GROWTH AND FEED EFFICIENCY**
4 **TRAITS IN RABBITS**

5
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11
12 **ABSTRACT**

13
14 Feed efficiency is a major production trait in animal genetic breeding schemes. To further
15 investigate the genetic control of feed efficiency in rabbits, we performed a genome wide
16 association study for growth and feed efficiency on 679 rabbits genotyped with the Affimetrix
17 Axiom Rabbit 200K Genotyping Array. After quality control, 127,847 SNPs were retained for
18 association analyses. The GWAS were performed using the GEMMA software, applying a mixed
19 univariate animal model with a linear regression on each SNP allele. The traits analysed were
20 weight at weaning and at 63 days of age, average daily gain, total individual feed intake, feed
21 conversion ratio and residual feed intake. No significant SNP was found for growth traits or feed
22 intake. Fifteen genome-wide significant SNPs were detected for feed conversion ratio on OCU7,
23 spanning from 124.8 Mbp to 126.3 Mbp, plus two isolated SNP on OCU2 (77.3 Mbp) and OCU8

24 (16.5 Mbp). For residual feed intake, a region on OCU18 (46.1-53.0 Mbp) was detected, which
25 contained a putative functional candidate gene, *GOT1*.

26

27 **Key words:** feed efficiency, SNP, GWAS, genetics, candidate genes, rabbits

28

29

INTRODUCTION

30

31 Improvement of feed efficiency is essential to increase the competitiveness of the rabbit industry
32 but also to reduce animal excretion, and consequently decrease the environmental impact of the
33 production (Gidenne *et al.*, 2017). Drouilhet *et al.* (2013, 2015) performed a selection to lower
34 residual feed intake (RFI) in rabbits. Heritability of RFI estimated by the authors was moderate
35 (0.16 (± 0.05)) (Drouilhet *et al.*, 2013). Recording accurately individual feed intake is costly and
36 time consuming, and large efforts are devoted in other species to facilitate the improvement of feed
37 efficiency by identifying genomic markers associated with this trait. Such approaches, including
38 linkage analyses, genome-wide association studies (GWAS) and candidate gene association
39 studies, have been performed to unravel the genetic background behind complex traits such as feed
40 efficiency in pigs (Onteru *et al.*, 2013; Ding *et al.*, 2018; Delpuech *et al.*, 2021). In rabbits,
41 following a first study for carcass traits (Sternstein *et al.*, 2015), association studies arose later,
42 with the recent availability of the Axiom Rabbit 200K Genotyping Array, and first results are now
43 available in various populations and traits, such as growth curve parameters
44 ([10.3389/fgene.2021.750939](https://doi.org/10.3389/fgene.2021.750939)), growth and carcass traits (doi: [10.3390/ani10061068](https://doi.org/10.3390/ani10061068)), litter size
45 (Sosa-Madrid *et al.*, 2020) and feed efficiency (Sánchez *et al.*, 2020). In this study, after estimating
46 genetic parameters to quantify the genetic basis of the traits in the design, GWAS was performed

47 on feed efficiency and growth traits in rabbits to identify genetic variants associated with these
48 traits, and candidate genes were searched for.

49

50

MATERIALS AND METHODS

51

Ethics statement

53

54 This study was carried out in accordance with the national regulations for animal care and use of
55 animals in agriculture, at the INRAE farm Pôle d'Expérimentation Cunicole Toulousain (Castanet-
56 Tolosan, France). It was reviewed and approved by the Animal Experimentation Ethics Committee
57 n°115 (agreement number APAFiS #18416), on behalf of the French Ministry for Higher
58 education, Research and Innovation.

59

Animals and phenotypes

61

62 The experimental rabbit population was issued from the paternal INRA 1001 line (Larzul and De
63 Rochambeau, 2005). Two related genetic lines were used in this design: the G10 line, selected for
64 10 generations for decreased RFI (Drouilhet *et al.*, 2013, 2015), and the G0 control line produced
65 from offspring of frozen embryos of the ancestor population of the selected line. The 296 G10 were
66 produced by mating 12 sires with 50 dams and the 292 G0 rabbits were produced by mating 10
67 sires and 51 dams in the same 3 batches, with a 42 days interval between batches. In each batch,
68 half of the kits was reared by G0 does and the second half was reared by G10 does. Litters were
69 made up by mixing 5 to 7 kits, each from different sire families of a given line. Does adopted

70 alternatively kits from one line and from the other line in successive batches. At weaning (32 days),
71 kits were placed in individual cages. From weaning to slaughtering, rabbits had free access to water
72 and *ad libitum* access to a diet with commercial pellets. Pellets were composed of 14.4% crude
73 protein, 27.9% acid detergent fibre, 9.9% acid detergent lignin, 8.8% crude ash, phosphorus
74 5.31 g/kg, zinc 100 mg/kg, copper 23.8 mg/kg. More details about the experiment can be found in
75 Garreau *et al.* (2019).

76 Animals were weighed at weaning (BW32) and at 63 days of age (BW63). Total individual feed
77 intake (FI) was recorded. Average daily gain (ADG) was obtained by dividing the body weight
78 gain during the test by the number of days of the growing period (31 days). Feed conversion ratio
79 (FCR) was calculated as total individual feed intake divided by the body weight gain. The RFI was
80 computed as the residual of the multiple linear regression of total individual feed intake on average
81 metabolic body weight (average body weight between weaning and end of the test to the power
82 0.75) to account for maintenance requirements, and ADG to account for production requirements
83 (REG procedure; SAS software), as in Drouilhet *et al.* (2015).

84

85 **Genotyping and genotype quality control**

86

87 Ear biopsies were sampled at 63 days of age. The DNA was extracted from ear biopsies of 711
88 animals (588 kits and their 123 parents), following a salt-based DNA extraction protocol. Six
89 hundred and ninety six animals were genotyped using the Affimetrix Axiom Rabbit 200K
90 Genotyping Array (Santa Clara, CA, USA) containing 199 692 SNPs, at the Centro Nacional de
91 Genotipado (CeGen) platform (Santiago de Compostela, Spain). The order and position of the
92 SNPs on the genome were based on the Rabbit OryCun2.0 assembly released by the Broad Institute
93 of MIT and Harvard (Carneiro *et al.*, 2014). The 11 mitochondrial SNPs were discarded from the

94 marker set, as well as 6267 and 7 SNPs located on sexual chromosomes X and Y, respectively. The
 95 QCF90 software (Masuda, 2020) was used for the quality control. Three successive steps are run.
 96 The first step disqualifies markers based on call rate, MAF and number of autosomal heterozygotes,
 97 leading to new allele frequency counts. In the second step, animals are examined, signaling those
 98 presenting a call rate below threshold and/or Mendelian conflicts. The final and third step is based
 99 on the estimation of gene content heritability and allows to discard markers with insufficient
 100 technical properties. Two rounds were carried out. First, with a threshold of 0.05 for MAF and 0.90
 101 for call rates, and second with a threshold of 0.95 for marker call rate, leading to a total of 686
 102 animals (568 tested progeny) and 128,226 remaining SNPs (i.e. an average of 1 SNP every 20 Kb)
 103 for further analyses.

104

105 **Statistical analyses**

106

107 The phenotypes of the 568 kits remaining after quality control were analyzed to test systematic
 108 effects using the GLM procedure (SAS Inst., Inc., Cary, NC). The fixed effects tested for each trait
 109 were: sex (2 levels), batch (3 levels), dam parity (4 levels), litter size at birth (4 levels : 1 to 5, 6-7,
 110 7-8, 9 and more) , litter size at weaning (4 levels : 1 to 4, 5, 6, 7 and more). The fixed effects were
 111 considered significant when P value ≤ 0.05 , and were included in the final model (Table 1).

112

113 **Table 1:** Significance¹ of the fixed effects in linear models for growth and feed efficiency traits

	BW32	BW63	ADG	FI	FCR	RFI
Sex	ns	**	**	*	ns	ns
Batch	***	***	**	***	***	***

Parity of dam	ns	ns	ns	ns	**	*
Litter size at birth	***	***	**	***	***	***
Litter size at weaning	***	***	ns	***	***	ns

114 BW32: BW at 32 days, BW63: body weight at 63 days, ADG: average daily gain, FI: total feed
 115 intake, FCR: feed conversion ratio, RFI: residual feed intake. ¹Significance levels from linear
 116 models including all effects *: $P < 0.05$; **: $P < 0.01$; ***: $P < 0.001$.

117

118 Estimation of genetic parameters

119

120 For the six traits of interest, heritabilities were computed with REML using the following univariate
 121 mixed model:

$$122 \quad \mathbf{y} = \mathbf{X}\mathbf{b} + \mathbf{Z}\mathbf{u} + \boldsymbol{\epsilon}$$

123 \mathbf{b} and \mathbf{u} are the vectors of estimated fixed and polygenic effects respectively and $\boldsymbol{\epsilon}$ is the vector of
 124 errors. \mathbf{y} , a vector of size equal to 586, represents the phenotypes, while \mathbf{Z} is the incidence matrix
 125 comprising indicators for the 1447 animals in the pedigree used to build the relationship matrix
 126 (*i.e.* up to the start of the above-mentioned selection for decreased RFI, thus encompassing
 127 common ancestors to the G0 and G10 populations). The blupf90+ software (Mizstal et al, 2014)
 128 was used to estimate variances, using genotype data in a ssGBLUP design (Mizstal et al, 2009),
 129 where the relationship matrix combined both pedigree and genomic information.

130

131 Genome wide association studies

132

133 The GWAS were performed using GEMMA version 0.94.1 (Zhou and Stevens, 2012). For each
134 trait, SNP effect a was successively tested at each position with the following animal mixed
135 model:

136

$$137 \mathbf{y} = \mathbf{X}\mathbf{b} + \mathbf{x}a + \mathbf{u} + \boldsymbol{\epsilon} \quad \text{with} \quad \mathbf{u} \sim N_n(\mathbf{0}, \mathbf{K}\sigma_u^2) \quad \text{and} \quad \boldsymbol{\epsilon} \sim N_n(\mathbf{0}, \mathbf{I}_n\sigma_\epsilon^2)$$

138

139 Where $N_n(\boldsymbol{\mu}, \mathbf{V})$ stands for a n -vector of Gaussian deviates of mean $\boldsymbol{\mu}$ and variance \mathbf{V} , \mathbf{y} is the
140 vector of phenotypes, \mathbf{X} is the incidence matrix of fixed effects and \mathbf{b} stands for the vector of these
141 effects, a is the marker effect and \mathbf{x} is the vector of marker genotypes, while \mathbf{u} is the vector of
142 random polygenic effect and $\boldsymbol{\epsilon}$ is the vector of errors. Residual effects are supposed independent.
143 Additive genetic effects were structured with \mathbf{K} , the centered relatedness matrix computed from
144 the genotypes and allele frequencies (VanRaden, 2008). Using the relationship matrix is aimed at
145 controlling the stratification and relatedness in the experimental population.

146

147 Significance was assessed for each tested SNP based on the P values of the Wald test. To account
148 for multiple testing, the significance threshold of the SNP P values was corrected via a Bonferroni
149 adjustment thanks to the SimpleM software (Gao et al., 2008, 2010). A principal component
150 analysis is applied to the correlation matrix between SNP genotypes. The number of independent
151 tests is assumed to be equal to the number of principal components retained to explain 99.5% of
152 variance. The number of independent tests was first calculated for each of the 21 autosomes
153 separately, and then summed to obtain the number of independent tests of the analysis. The total
154 number of independent tests was 3 804 for the 128,226 retained SNPs. Therefore, the genome-wide
155 significance threshold for $-\log_{10}(P \text{ values})$ was equal to 4.83.

156 Each set of SNPs with $-\log_{10}(P \text{ values})$ above the threshold evidenced a region which could be
157 characterized by the number of SNPs, their positions, and the proportion of variance explained by
158 the leading SNP (i.e. the SNP exhibiting the largest score). The variance explained by the leading
159 SNP is $V_{SNP} = 2 \times p \times (1 - p) \times a^2$, where, as above, a is the marker effect while p is the allele
160 frequency.

161

162 **RESULTS AND DISCUSSION**

163

164 **Heritability estimates**

165

166 Heritability estimates ranged between 0.14 ± 0.06 and 0.33 ± 0.07 for growth traits and between
167 0.40 ± 0.07 and 0.47 ± 0.06 for feed intake and efficiency traits (table 2). These estimates were
168 higher than those reported by Drouilhet *et al.* (2013) for the same traits from data recorded during
169 the first 6 generations of selection in the same rabbit experimental line selected for RFI. In other
170 rabbit lines under ad libitum feeding, heritability estimates of ADG ranged from 0.11 ± 0.02 (Piles
171 and Blasco, 2003) to 0.41 ± 0.13 (Larzul and De Rochambeau, 2005). Lower heritabilities were
172 also reported for FCR in the literature: 0.25 ± 0.12 (line R; Piles et al., 2004) and 0.31 ± 0.10 (line
173 C; Piles et al., 2004). The high values of heritability estimated in our study for feed efficiency traits
174 can be explained by the specific composition of our experimental population, composed of half by
175 rabbits selected for RFI and of the other half by non-selected rabbits, thus gathering two connected
176 but genetically different populations.

177

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

179

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

180

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

183

184 **GWAS results**

185

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

196

197 **Table 3:** Characteristics of the evidenced regions for a putative QTL influencing FCR and RFI.

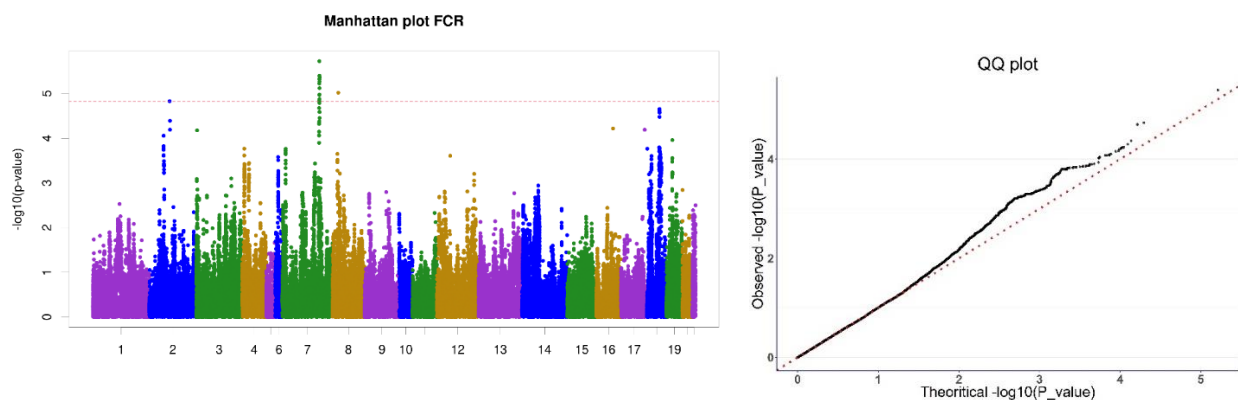
Trait	FCR	FCR	FCR	RFI
Chromosome	2	7	8	18
Number of SNPs	1	15	1	111
Position min (Mbp)	77.3	124.8	16.5	46.1
Position max (Mbp)	77.3	126.3	16.5	53.0
Position of leading SNP	77.3	124.9	16.5	48.3
-Log ₁₀ Pval of leading SNP	4.83	5.73	5.02	6.30
Percentage of variance explained by the leading SNP	2.73%	4.53%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

199

200

201 Despite the limited annotation of the rabbit genome, a putative functional candidate gene, *GOT1*
202 (47.39-47.42 Mbp), was identified in this region. Glutamic-oxaloacetic transaminase is a pyridoxal
203 phosphate-dependent enzyme that exists in cytoplasmic mitochondrial forms. *GOT1* plays a role
204 in amino acid metabolism and in urea and tricarboxylic acid cycles (Mavrides & Christen 1978).
205 A significant positive correlation between RFI and fecal N was described by Aggrey *et al.* (2014)

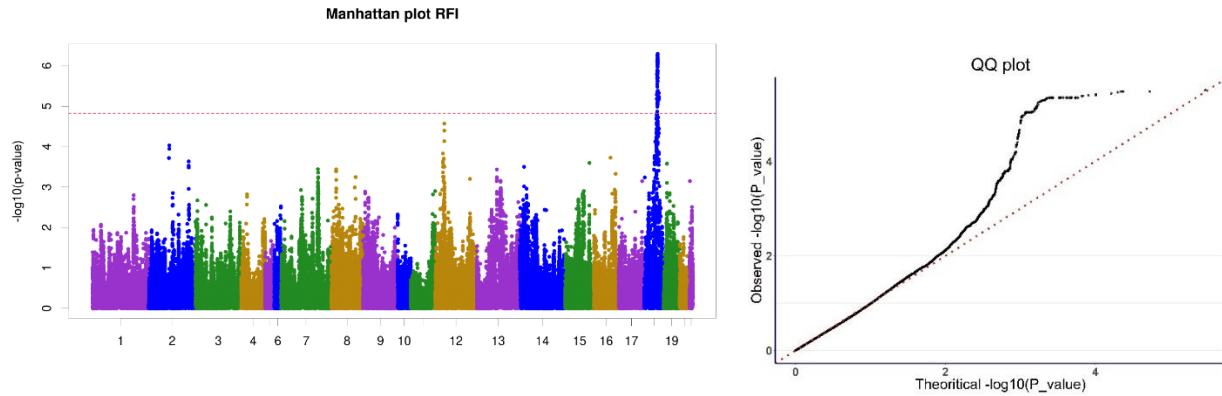
206 in broilers: the birds in the LRFI population attained greater feed efficiency by having lower FI,
207 increasing their protein retention and, consequently, reducing fecal N. The same authors reported
208 different gene expression levels of *GOT1* between two broilers lines divergently selected for RFI.
209 *GOT1* was downregulated in four tissues (duodenum, muscle, liver and kidney) of the low RFI
210 line. Mukiibi *et al.* (2018) also found differential expression of *GOT1* between six extreme high
211 and six extreme low RFI steers from three beef breed populations. The role of this gene in the
212 metabolism of amino acids and urea is fully consistent with the results obtained from the
213 comparison of the two lines that compose our experimental population (Gidenne et al, 2015): the
214 N balance was improved in the G10 selected line compared to the G0 non selected line (+5%),
215 leading to a reduced N output either through the feces (meanly -6 g/d compared to G0) or the urine
216 (-0.07 g/d), and to an improved N retention ratio (+3% compared to G0).



217
218 **Figure 1:** Manhattan plot (left) and Quantile-Quantile (QQ, right) plot for FCR. Dashed line
219 corresponds to the 5% genome-wide threshold. The dotted line on the QQ plot corresponds to the
220 $y=x$ line.

221

222



223

224 **Figure 2:** Manhattan plot and Quantile-Quantile (QQ) plot for RFI. Dashed line corresponds to
 225 the 5% genome-wide threshold. The dotted line on the QQ plot corresponds to the $y=x$ line.

226

227 In rabbits, very few QTL have been described in the literature. Sanchez *et al.* (2020) revealed a
 228 total of 189 SNPs significantly associated with ADG and feed efficiency traits, in 17 chromosomal
 229 regions but not on the chromosomes 7 or 18 revealed by our study. In 12 of the regions identified
 230 by these authors, 20 candidate genes were proposed to explain the variation of the analyzed traits,
 231 including genes such as *FTO*, *NDUFAF6* and *CEBPA* previously reported as associated with
 232 growth and feed efficiency traits in monogastric species. A total of 28, 81 and 10 significant SNPs
 233 were identified by Yang *et al.* (2020) for growth, carcass and meat quality traits, respectively, but
 234 the QTLs were located on different chromosomes than those identified in our study. Additionally,
 235 16, 71 and 9 candidate genes within 100 kb upstream or downstream of these SNPs were proposed
 236 by the authors. Several candidate genes have been proposed in other studies for body weight at
 237 different ages (Zhang *et al.*, 2013; Helal *et al.*, 2019; Helal *et al.*, 2022; Yang *et al.*, 2019) and meat
 238 quality (Zhang *et al.*, 2013; Helal *et al.*, 2019; Helal *et al.*, 2022; Yang *et al.*, 2019; El-Sabroun *et al.*,
 239 *et al.*, 2018). Growth hormone genes (*GH*, *GHR*), insulin-like growth factor 2 gene (*IGF2*) and

240 myostatin gene (*MSTN*) were the most frequent genes associated with growth and meat quality, but
241 they were not in the vicinity of the regions detected in the present study.

242

243

244

CONCLUSIONS

245

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

254

255

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256

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260

261

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