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

Hervé Garreau, Yann Labrune, Hervé Chapuis, Julien Ruesche, Juliette Riquet, Julie Demars, Florence Benitez, François Richard, Laurence Drouilhet, Olivier Zemb, et al.

Running Head: GWAS analyses for growth and feed efficiency

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

Garreau H.*, Labrune Y., Chapuis H., Ruesche J., Riquet J., Demars J., Benitez F., Richard F., Drouilhet L., Zemb O., Gilbert H.

GenPhySE, Université de Toulouse, INRAE, F-31326 Castanet-Tolosan, France

*Corresponding author: herve.garreau@inrae.fr

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 for growth and feed efficiency on 679 rabbits genotyped with the Affimetrix Axiom Rabbit 200K Genotyping Array. After quality control, 127,847 SNPs were retained for association analyses. The GWAS were performed using the 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 the production (Gidenne *et al*., 2017). 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). Recording accurately individual feed intake is costly and time consuming, and large efforts are devoted 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 (10.3389/fgene.2021.750939), growth and carcass traits (doi: 10.3390/ani10061068), 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.

MATERIALS 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 #18416), 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 sires with 50 dams and the 292 G0 rabbits were produced by mating 10 sires and 51 dams in the same 3 batches, with a 42 days interval between batches. In each batch, half of the kits was reared by G0 does and the second half was 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

alternatively kits from one line and from the other line in successive batches. At weaning (32 days), 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, 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 days 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 days). 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 days 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 SNPs, 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, 2020) 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, signaling 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 to discard markers with insufficient technical properties. Two rounds were carried out. First, with a threshold of 0.05 for 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 analyzed 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), 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).

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	***	***	**	***	***	***

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

BW32: BW at 32 days, BW63: body weight at 63 days, 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 *: $P < 0.05$; **: $P < 0.01$; ***: $P < 0.001$.

Estimation of genetic parameters

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

$$\boldsymbol{y} = \boldsymbol{Xb} + \boldsymbol{Zu} + \boldsymbol{\epsilon}$$

$\boldsymbol{b}$ and $\boldsymbol{u}$ are the vectors of estimated fixed and polygenic effects respectively and $\boldsymbol{\epsilon}$ is the vector of errors. $\boldsymbol{y}$, a vector of size equal to 586, represents the phenotypes, while $\mathbf{Z}$ 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:

$$\boldsymbol{y} = \boldsymbol{Xb} + \boldsymbol{x}a + \boldsymbol{u} + \boldsymbol{\epsilon} \qquad \text{with} \quad \boldsymbol{u} \sim \mathrm{N}_{\boldsymbol{n}}(\mathbf{0}, \mathbf{K}\sigma_u^2) \qquad \text{and} \quad \boldsymbol{\epsilon} \sim \mathrm{N}_{\boldsymbol{n}}(\mathbf{0}, \mathbf{I_n}\sigma_\epsilon^2)$$

Where $\mathrm{N}_{\boldsymbol{n}}(\boldsymbol{\mu}, \mathbf{V})$ stands for a *n*-vector of Gaussian deviates of mean $\boldsymbol{\mu}$ and variance $\mathbf{V}$, $\boldsymbol{y}$ is the vector of phenotypes , $\boldsymbol{X}$ is the incidence matrix of fixed effects and $\boldsymbol{b}$ stands for the vector of these effects, a is the marker effect and $\boldsymbol{x}$ is the vector of marker genotypes, while $\boldsymbol{u}$ is the vector of random polygenic effect and $\boldsymbol{\epsilon}$ is the vector of errors. Residual effects are supposed independent. Additive genetic effects were structured with **K**, the centered relatedness matrix computed from the genotypes and allele frequencies (VanRaden, 2008). Using the relationship matrix is aimed at controlling 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 3 804 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 characterized 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.

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, composed of half by rabbits selected for RFI and of the other half by non-selected rabbits, thus gathering two connected but genetically different populations.

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

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 compared to expectation, validating the control of the population structure in our analyses.

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

198

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)

in broilers: the birds in the LRFI population attained greater feed efficiency by having lower FI, increasing their protein retention and, consequently, reducing fecal N. The same authors reported different gene expression levels of *GOT1* between two broilers 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 extreme high and six extreme 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, 2015): 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 feces (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).

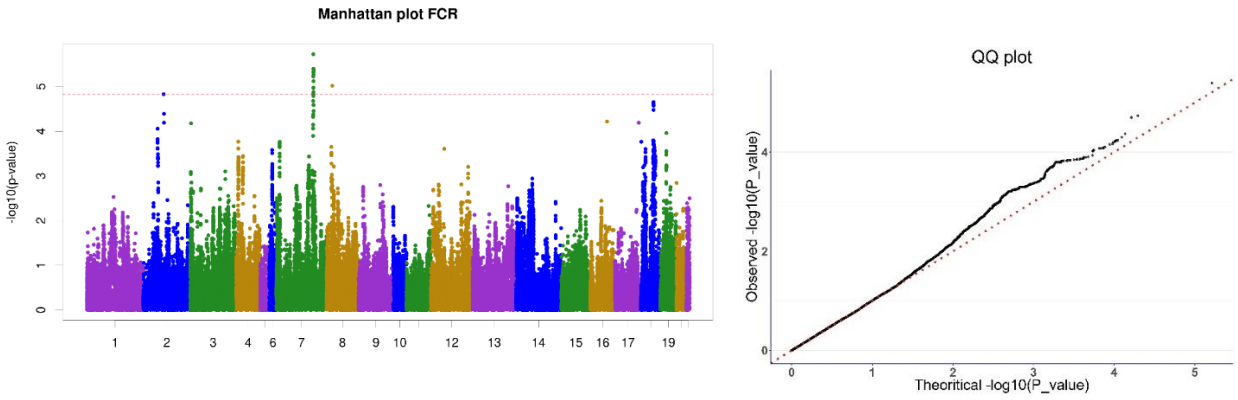
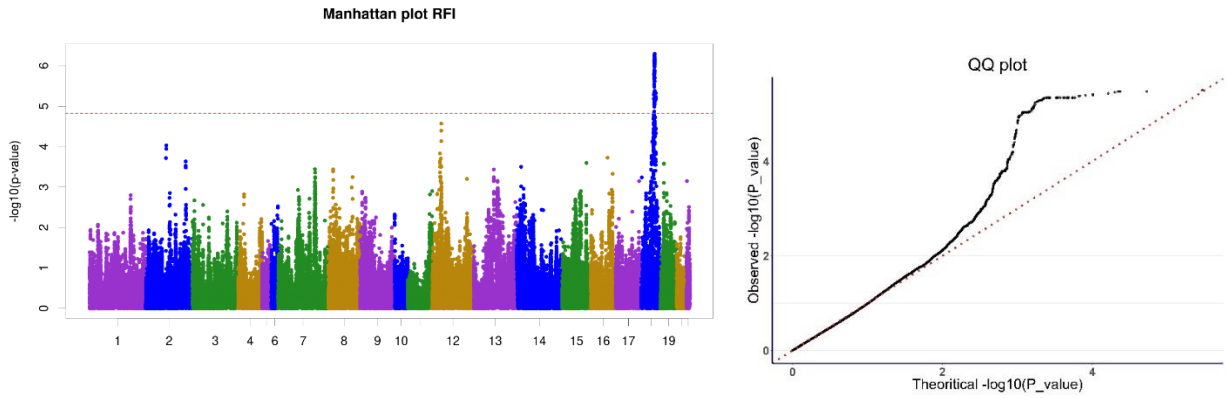


Figure 1: Manhattan plot (left) and Quantile-Quantile (QQ, right) plot for FCR**.** Dashed line corresponds to the 5% genome-wide theshold. The dotted line on the QQ plot corresponds to the y=x line.



223

224 **Figure 2:** Manhattan plot and Quantile-Quantile (QQ) plot for RFI**.** Dashed line corresponds to
225 the 5% genome-wide theshold. 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 litterature. 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-Sabrout et
239 al., 2018). 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.

CONCLUSIONS

A genome association study was performed in an experimental population which 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.

ACKNOWLEDGEMENTS

This study is part of the Feed-a-Gene Project, funded from the European Union's H2020 Programme under grant agreement no 633531. We acknowledge the CRAG for the genotyping and the staff of the PECTOUL experimental farm for the animal raising and the data recording.

REFERENCE LIST

Aggrey S.E., Lee J., Karnuah A.B. and Rekaya R. 2014. Transcriptomic analysis of genes in the nitrogen recycling pathway of meat-type chickens divergently selected for feed efficiency. *Anim. Genet*., 45, 215 – 222. https://doi.org/10.1111/age.12098

Carneiro M., Rubin C.J., Di Palma F., Albert F.W., Alföldi J., Barrio A.M., Pielberg G., Rafati N., Sayyab S., Turner-Maier J., Younis S., Afonso S., Aken B., Alves J.M., Barrell D., Bolet G., Boucher S., Burbano H.A., Campos R., Chang J.L., Duranthon V., Fontanesi L., Garreau H., Heiman D., Johnson J., Mage R.G., Peng Z., Queney G., Rogel Gaillard C., Ruffier M., Searle S., Villafuerte R., Xiong A., Young S., Forsberg-Nilsson K., Good J.M., Lander E.S., Ferrand N., Lindblad-Toh K., Andersson L. 2014. Rabbit genome analysis reveals a polygenic basis for phenotypic change during domestication. *Science*, 345, 1074-1079. doi: 10.1126/science.1253714

Delpuech E., Aliakbari A., Labrune Y., Fève K., Billon Y., *et al.* 2021. Identification of genomic regions affecting production traits in pigs divergently selected for feed efficiency. *Genet. Sel. Evol.*, 53 (1). 10.1186/s12711-021-00642-1.

Ding R., Yang M., Wang X., Quan J., Zhuang Z., Zhou S., et al. Genetic architecture of feeding behavior and feed efficiency in a Duroc pig population. *Front Genet.* 2018;9:220.

Drouilhet L., Gilbert H., Balmisse E., Ruesche J., Tircazes A., Larzul C., Garreau H. 2013. Genetic parameters for two selection criteria for feed efficiency in rabbits. *J. Anim. Sci.* 91, 3121–3128. https://doi.org/10.2527/jas.2012-6176

Drouilhet L., Achard C.S, Zemb O., Molette C., Gidenne T., Larzul C., Ruesche J., Tircazes A., Segura M., Theau-Clément M., Joly T., Balmisse E., Garreau H., Gilbert H. 2015. Direct and correlated responses to selection in two lines of rabbits selected for feed efficiency under ad libitum and restricted feeding: I. Production traits and gut microbiota characteristics. *J. Anim. Sci.*, doi: 10.2527/jas2015-9402.

El-Sabrout, K.and Aggag, S. (2018). Association of Melanocortin (MC4R) and Myostatin (MSTN) genes with carcass quality in rabbit. *Meat Science*, 137, 67-70.

Garreau, H., Ruesche, J., Gilbert, H., Balmisse, E., Benitez, F., Richard, F., David, I., Drouilhet, L., Zemb, O. 2019. Estimating direct genetic and maternal effects affecting rabbit growth and feed efficiency with a factorial design. *J. Anim. Breed. Genet*., 136 (3), 168-173. doi: 10.1111/jbg.12380

Gidenne T., Lamothe L., Bannelier C., Molette C., Gilbert H., Chemit M.L., Segura M., Benitez F., Richard F., Garreau H., Drouilhet L. 2015. Direct and correlated responses to selection in two lines of rabbits selected for feed efficiency under ad libitum and restricted feeding: I. Production traits and gut microbiota characteristics. *J. Anim. Sci.*, doi : 10.2527/jas2015-9402

Gidenne T., Garreau H., Drouilhet L., Aubert C., Maertens L. 2017. Improving feed efficiency in rabbit production, a review on nutritional, technico-economical, genetic and environmental aspects. *Anim. Feed Sci. Technol*., 225, pp.109-122. 10.1016/j.anifeedsci.2017.01.016

Helal, M. M. 2019. Association between growth hormone receptor gene polymorphism and body weight in growing rabbits. *Adv. Anim. Vet. Sci.*, 7(11), 994-998.

Helal, M., Hany, N., Maged, M., Abdelaziz, M., Osama, N., Younan, Y. W., Ismail, Y., Abdelrahman, R., Ragab, M. 2021. Candidate genes for marker-assisted selection for growth, carcass and meat quality traits in rabbits. *Animal Biotechnology*, 33(7), 1691-1710.

Mavrides C. and Christen P. 1978. Mitochondrial and cytosolic aspartate aminotransferase from chicken: activity towards amino acids. *Biochem. Biophys. Res. Comm.* 85, 769–73.

Misztal, I., Legarra, A., Aguilar, I. 2009. Computing procedures for genetic evaluation including phenotypic, full pedigree, and genomic information. *J. Dairy Sci.*, 92, 4648–4655.

Misztal, I., S. Tsuruta, D.A.L. Lourenco, I. Aguilar, A. Legarra, and Z. Vitezica. 2014. Manual for BLUPF90 family of programs.

http://nce.ads.uga.edu/wiki/lib/exe/fetch.php?media=blupf90_all2.pdf

Mukiibi R., Vinsky M., Keogh K. A., Fitzsimmons C., Stothard P., Waters S. M., et al. 2018. Transcriptome analyses reveal reduced hepatic lipid synthesis and accumulation in more feed efficient beef cattle. *Sci. Rep.* 8(1), 7303. doi: 10.1038/s41598-018-25605-3

Onteru SK, Gorbach DM, Young JM, Garrick DJ, Dekkers JCM, Rothschild MF. Whole genome association studies of residual feed intake and related traits in the pig. *PLoS One*. 2013;8:e61756.

Piles, M., Blasco, A. 2003. Response to selection for growth rate in rabbits estimated by using a control cryopreserved population. *World Rabbit Sci.,* 11, 53-62.

Piles, M., Gomez, E.A., Rafel, O., Ramon, J., Blasco, A. 2004. Elliptical selection experiment for the estimation of genetic parameters of the growth rate and feed conversion ratio in rabbits. *J. Anim. Sci.*, 82, 654-660.

Purcell S., Neale B., Todd-Brown K., Thomas L., Ferreira M.A.R., Bender D., Maller J., Sklar P., de Bakker P.I.W., Daly M.J., Sham P.C. 2007. PLINK: a toolset for whole-genome association and population-based linkage analysis. *Am. J. Hum. Genet.*, 81(3), 559–575.

Sánchez, J. P., Legarra, A., Velasco-Galilea, M., Piles, M., Sánchez, A., Rafel, O., et al. 2020. Genome-wide association study for feed efficiency in collective cage-raised rabbits under full and restricted feeding. *Anim. Genet.* 51, 799–810. doi: 10.1111/age.12988.

Sosa-Madrid B.S., Santacreu M.A., Blasco A., Fontanesi L., Pena R.N., Ibanez-Escriche N. 2020. A genomewide association study in divergently selected lines in rabbits reveals novel genomic regions associated with litter size traits. *J Anim Breed Genet.* 137:123–38.

Sternstein, I., Reissmann M., D., Dorota M., Bieniek J., Brockmann G. A. 2015. "A comprehensive linkage map and QTL map for carcass traits in a cross between Giant Grey and New Zealand White rabbits." BMC Genetics, 16 (1): 16.

334 VanRaden, P.M. 2008. Efficient Methods to Compute Genomic Predictions. *Journal of Dairy*
335 *Science*, 91, 4414-4423.
336 Yang, L. Q., Zhang, K., Wu, Q. Y., Li, J., Lai, S. J., Song, T. Z., & Zhang, M. 2019.
337 Identification of two novel single nucleotide polymorphism sites in the Myostatin (MSTN)
338 gene and their association with carcass traits in meat-type rabbits (Oryctolagus cuniculus).
339 World Rabbit Science, 27(4), 249-256.
340 Yang, X., Deng, F., Wu, Z., Chen, S. Y., Shi, Y., Jia, X., & Lai, S. J. (2020). A Genome-Wide
341 Association Study Identifying Genetic Variants Associated with Growth, Carcass and Meat
342 Quality Traits in Rabbits. *Animals*, 10(6), 1068.
343 Zhang, G. W., Gao, L., Chen, S. Y., Zhao, X. B., Tian, Y. F., Wang, X., ... & Lai, S. J. 2013.
344 Single nucleotide polymorphisms in the FTO gene and their association with growth and
345 meat quality traits in rabbits. *Gene*, 527(2), 553-557.
346 Zhou X., Stephens M. 2012. Genome-wide efficient mixed-model analysis for association studies.
347 *Nat. Genet*. 44: 821-824. doi: 10.1038/ng.2310