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GENETIC FACTORS OF FUNCTIONAL TRAITS

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Abstract: Selection of functional traits is a challenge for researchers, but an increasingly necessary objective due to the growing concern regarding animal welfare and overcoming the problems of reducing antibiotic use in rabbit production without undermining the animals' productivity. The aim of this review is to discuss the genetic control of resistance to diseases, longevity and variability of birth weight within a litter, or litter size variability at birth within doe, describing the selection programmes and the first results from a multi-omics analysis of resistance/susceptibility to diseases. The heritability is around 0.13 for longevity, 0.01 for uniformity in birth weight, 0.09 for litter size variability and around 0.11 for disease resistance. Genetic correlations between functional traits and production traits are mostly no different from zero, or are moderately favourable in some cases. Six selection programmes developed in three countries are reviewed. Line foundation with high pressure for selection or divergent selection experiments are different methodologies used, and favourable responses to selection have been achieved. Genomics studies have revealed associations in regions related to immune system functionality and stress in lines selected for litter size variability. Knowledge of the role of gut microbiota in the rabbit's immune response is very limited. A multi-omics approach can help determine the microbial mechanisms in regulation immunity genes of the host.

Key Words: genetic, longevity, omics, resilience, resistance to diseases, selection, rabbit.

INTRODUCTION

Breeding programmes have played an important role in improving efficiency in meat rabbit production. Traditionally, maternal lines are selected for litter size at birth or at weaning (Baselga, 2004) and paternal lines are selected for post-weaning growth rate or body weight at a point close to market age (Rochambeau *et al.*, 1989; Lukefahr *et al.*, 1996; Piles and Blasco, 2003; Larzul *et al.*, 2005). Other traits have been studied as criteria in breeding programmes, either in maternal lines, such as ovulation rate and kit survival (Piles *et al.* 2006; Ziadi *et al.*, 2013), or in paternal, such as carcass dressing percentage, thigh muscle volume, intramuscular fat, food efficiency and heat tolerance (Zomeño *et al.*, 2013; Matics *et al.*, 2014; Piles *et al.*, 2014, Piles and Sánchez, 2019). Nowadays, priorities in rabbit breeding are related to improving animal welfare and disease resistance, which leads to better adaptation of females to changing environmental conditions.

Functional traits are used to summarise those characters of an animal that increase efficiency by reducing input costs. Major groups of breeding goal traits belonging to this category are health, fertility or longevity (Groen *et al.*, 1997). Functional traits determine the response to environmental factors (Reiss *et al.*, 2009). Therefore, robustness, rusticity, resilience, plasticity and resistance to diseases are concepts related to them.

The notion of robustness refers to the combination of high production potential and low sensitivity to environmental perturbations. The importance of robustness-related traits in breeding objectives is progressively increasing towards the production of animals with a high production level in a wide range of climatic conditions and production systems

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(Knap, 2005), together with a high level of animal welfare (Mormede and Terenina, 2012). When an animal has the ability to adapt to an unfavourable environment, but without the requirement of maintaining a high production level, rusticity is defined (Sauvant and Martin, 2010). Colditz and Hine (2016) defined resilience in animal production as the animal's capacity to be minimally affected by disturbances or to rapidly return to the state it was in before exposure to a disturbance.

Both robustness and resilience refer to the ability of an animal to survive disruptions. However, robustness is considered a static concept where the animal can resist disruptions and retain its previous stable situation, whereas resilience is more of a dynamic concept incorporating adaptation, where an animal can return to a new stable situation after surviving a threat. Therefore, resilience is also related to plasticity.

Genetic selection of functional traits has been used to increase robustness in pigs (Knap, 2005), poultry (Star *et al.*, 2008) and rabbits (Sánchez *et al.*, 2008; Garreau *et al.*, 2017). Recently, environmental variance has been proposed as a measure of resilience (Berghof *et al.*, 2019). Many studies have provided statistical evidence that environmental variance is partly under genetic control (mice, Ibáñez-Escriche *et al.*, 2008a; pigs, Ibáñez-Escriche *et al.*, 2008b; chickens, Mulder *et al.*, 2009) and selection experiments support these findings in rabbits (for birth weight variability, Bolet *et al.*, 2007; for litter size variability, Blasco *et al.*, 2017) and mouse (for birth weight variability, Formoso-Rafferty *et al.*, 2016).

The main objective of this review is to discuss the genetic control of longevity, disease resistance traits and variability of birth weight and litter size, presenting the selection programmes with inclusion of these traits and describing the first results from a multi-omics analysis of resistance/susceptibility to diseases.

GENETIC CONTROL OF FUNCTIONAL TRAITS

Genetic variability is the prerequisite for any breeding programme. In rabbits, the first studies to determine whether disease resistance was heritable began in 1969 in Australia, then in 1988 in Europe (Sobey, 1969; Baselga *et al.*, 1988). Analyses of longevity began in the 2000s, while the study of the genetic parameters of homogeneity traits was initiated in 2008. Longevity and homogeneity of birth weight or litter size were studied in maternal rabbit lines, while disease resistance traits were studied in both paternal and maternal lines.

The heritability of longevity is around 0.13, varying from 0.02 to 0.24 (Table 1). Heritability of the homogeneity traits is low, 0.01 for the uniformity in birth weight within a litter and 0.08 for the litter size variability at birth within a doe

Table 1: Heritability for longevity.

Trait definition	Heritability	Model	Country	Line/breed	Authors
Length of lifetime ¹	0.13	Linear model	Germany	New Zealand white	Youssef <i>et al.</i> , 2000
Number of AI ²	0.10	Weibull	France	INRA 1077	Garreau <i>et al.</i> , 2001
Number of AI ²	0.05	Discrete model	France	INRA 1077	Garreau <i>et al.</i> , 2001
Length of lifetime ³	0.05	Cox model	Spain	V line	Sánchez <i>et al.</i> , 2004
Length of lifetime ⁴	0.10	Cox model	Spain	V line	Sánchez <i>et al.</i> , 2006
Length of lifetime ³	0.16 to 0.24	Cox model	Spain	Prat	Piles <i>et al.</i> , 2006
Number of AI ²	0.17 to 0.19	Discrete model	France	INRA 1077	Piles <i>et al.</i> , 2006
Number of AI ²	0.12	Discrete model	France	Hycrole line D	Lenoir <i>et al.</i> , 2013
Functional longevity ⁵	0.07	Cox model	Spain	A line	El Nagar <i>et al.</i> , 2020
Functional longevity ⁵	0.03	Cox model	Spain	V line	El Nagar <i>et al.</i> , 2020
Functional longevity ⁵	0.14	Cox model	Spain	H line	El Nagar <i>et al.</i> , 2020
Functional longevity ⁵	0.05	Cox model	Spain	LP line	El Nagar <i>et al.</i> , 2020
Functional longevity ⁵	0.02	Cox model	Spain	R line	El Nagar <i>et al.</i> , 2020

¹Longevity is defined as: the length of lifetime production in months. ²The total number of artificial inseminations (AI) performed after the first kindling or death. ³Date of the first presentation to a male and the data of death or culling. ⁴The time in days between date of the first positive pregnancy diagnosis and date of culling. ⁵Difference between the date of the first positive palpation test and the date of death or culling due to involuntary cause.

Table 2: Heritability (diagonal) and genetic correlation (above) of variability and mean of birth weight and litter size.

Trait	Variability	Mean	Country	Line	Authors
Birth weight ¹	0.012 (0.004) ³	0.085 (0.066) 0.060 (0.011)	France	AGP22	Garreau <i>et al.</i> , 2008a, Bodin <i>et al.</i> , 2010b
Litter size ²	0.08 (0.05; 0.11) ⁴	-0.06 (-0.31; 0.21) 0.10 (0.08; 0.13)	Spain	Maternal	Blasco <i>et al.</i> , 2017

¹Within-litter standard deviation. ²Environmental variability. ³Standard error. ⁴High density posterior interval at 95%.

(Table 2). Heritability of the resistance traits varies from 0.02 to 0.64 depending on the disease, its prevalence and the model used (Table 3). On average, the heritability of disease resistance is around 0.11 on the observed scale and 0.15 on the underlying scale. In summary, the heritability of these traits tends to be low to moderate.

Genetic correlations between longevity and productive traits were estimated using approximation methods (Sánchez *et al.*, 2006; Lenoir *et al.*, 2013). Negative correlations are favourable; they indicate a lower risk of death or culling for the rabbits with a higher value of the production traits. The correlation between longevity and litter traits or adult weight were either not significantly different from zero or favourable, although the standard errors are missing (Table 4).

The genetic correlations between the mean and the variability for birth weight and litter size were no different from zero (Table 2). Genetic correlations between resistance to diseases and production traits are either favourable or no different from zero (Table 5). There is evidence that genetic correlation between resistance to different illnesses and production traits decreases over time, so the estimates are higher for daily gain before weaning (Shrestha *et al.*, 2019) than for direct weaning weight (Gunia *et al.*, 2018) and daily gain during the fattening period (Ragab *et al.*, 2015). Finally, genetic correlation is no different from zero for weight at the end of the fattening period (Gunia *et al.*, 2015). The resistance to digestive disorders is favourably correlated with the carcass yield and no different from zero for litter size (Gunia *et al.*, 2015; 2018).

To summarise, the heritabilities tend to be low to moderate. The genetic correlations between functional traits and production traits are mostly not significantly different from zero, or are favourable in some cases. The possible independence of functional and production traits means that functional traits can be included in a breeding programme without trade-offs.

SELECTION PROGRAMMES AND RESPONSE TO SELECTION

The first approach to selection for disease resistance was a mass selection programme for resistance to myxomatosis, conducted from 1955 to 1967 in Australia (Sobey, 1969). Four virus strains were used and rabbits were infected with the appropriate virus after 16 wk of age, to obviate the effects of maternal antibodies. Percentage of recovery increased from 50 to 80% for the least virulent strain and from 10 to 20% for the most virulent virus strain.

A maternal line (LP line) was constituted following a longevity criterion at the Polytechnic University of Valencia (Spain, Sánchez *et al.*, 2008). Then, the selection was carried out by litter size at weaning. The foundation process of the LP line was inspired by the hyperprolific selection experiments proposed and carried out by the same research group (Cifre *et al.*, 1998). Thus, the LP line was founded by selecting females from commercial farms that showed extremely high productive lives (between 25 and 41 parities) and whose prolificacy ranged from 7.5 to 11.9 young born alive (Sánchez *et al.*, 2008). When the LP line was compared to the V line selected for litter size at weaning for 31 non-overlapping generations, the LP line was 1.3 times less likely to leave the herd than the V line, demonstrating the longer productive life of the LP line (Sánchez *et al.*, 2008) and similar productivity from the fourth parity onwards in both lines (Theilgaard *et al.*, 2007).

The ability of the LP line to sustain reproduction in the different environments without presenting great mobilisation of body reserves and its ability to use reserves at the onset of feed constraints seems to be a safeguarding factor to ensure longevity (Theilgaard *et al.*, 2009; Savietto *et al.*, 2013, 2015). Moreover, the LP line presented higher lymphocyte counts under heat stress conditions than the V line (Ferrian *et al.*, 2012), and before and

Table 3: Heritability (standard errors) for disease resistance traits¹.

Disease or syndromes	Trait description	Variable type	Heritability		Country	Line/breed	Type of line	Authors
			Linear model ³	Threshold model				
Myxomatosis after experimental infection	Survival time (days)	continuous	0.33 to 0.64		Australia	domestic rabbits	-	Sobey, 1969
Respiratory infection caused by <i>Pasteurella multocida</i> and <i>Bordetella bronchiseptica</i>	Survival to myxomatosis	0-1	0.07 (0.03) to 0.18 (0.09)	0.36	Spain	A.V.R.B	maternal and paternal	Baseiga <i>et al.</i> , 1988
Bacterial infection caused by <i>Pasteurella multocida</i> or <i>Staphylococcus aureus</i>	Extension of lesions on lung lobes	0-5	0.12 (0.05) to 0.28 (0.14)					
	Average score of lung lesions	0-5	0.03 (0.01) to 0.04 (0.01)	0.13 (0.04) to 0.38 (0.11)	France	2 commercial populations	paternal	Eady <i>et al.</i> , 2004
	Incidence of infection	0-1	0.02 (0.02) to 0.06 (0.02)	0.06 (0.05) to 0.12 (0.05)	Australia	composite strain	-	Eady <i>et al.</i> , 2007
	Weekly incidence of infection	0-1						
	Overall incidence of infection	0-1	0.06 (0.02)	0.05 (0.03)				
	Overall Mortality from infection	0-1		0.02 (0.05)				
Pasteurellosis after experimental infection	Extent of abscess dissemination	0-5	0.11 (0.06)		France	INRA 1777 and 6 commercial populations	maternal	Shrestha <i>et al.</i> , 2018
	Extent of bacteria dissemination	0-5	0.09 (0.05)					
	Resistance: combination of survival, abscess and bacteria scores	0-5	0.14 (0.05)					
ERE ² after experimental infection	Mortality	0-1		0.05 (0.05)	France	INRA 1777	maternal	Garreau <i>et al.</i> , 2006
	Resilience (alive and normal growth)	0-1		0.38 (0.21)				
	Diarrhoea	0-1		0.21 (0.16)				
	Abnormal growth	0-1		0.08 (0.07)				
Non-specific syndromes	Non-specific mortality	0-1	0.07 (0.02) to 0.10 (0.02)	0.27 (0.06) to 0.30 (0.06)	Spain	Caldes	paternal	Ragab <i>et al.</i> , 2015
	Morbidity and mortality from ERE ²	0-1	0.05 (0.02) to 0.06 (0.02)	0.17 (0.09)				
	Respiratory syndromes	0-1	0.03 (0.01)	0.23 (0.05) to 0.27 (0.08)				
	Poor body condition score	0-1	0.03 (0.02) to 0.06 (0.02)	0.20 (0.06) to 0.38 (0.09)				
	Digestive disorders	0-1	0.03 (0.00) to 0.11 (0.03)	0.08 (0.02)	France	AGP39, AGP59, AGP77	paternal and maternal	Garreau <i>et al.</i> , 2008b. Gunia <i>et al.</i> , 2015, 2018
	Respiratory disorders	0-1	0.04 (0.00) to 0.09 (0.02)					
	Infectious disease	0-1	0.03 (0.00) to 0.08 (0.02)					

¹Traits are recorded under natural infection; unless otherwise stated. ²Epizootic Rabbit Enteropathy. ³Linear model (or results of threshold models expressed on the observed scales).

Table 4: Pseudo-genetic correlations (standard error) between longevity and production traits.

Trait	Pseudo-Genetic correlation	Authors
Number of kits born alive	0.16 (0.10)	Sánchez <i>et al.</i> , 2006 ¹
Number of kits born alive	-0.72	Lenoir <i>et al.</i> , 2013 ²
Number of kits at weaning	-0.17 (0.11)	Sánchez <i>et al.</i> , 2006
Litter weight at weaning	-0.7	Lenoir <i>et al.</i> , 2013
Teat number	-0.39	Lenoir <i>et al.</i> , 2013
Adult weight	-0.2	Lenoir <i>et al.</i> , 2013

Longevity is defined as: ¹the time in days between date of the first positive pregnancy diagnosis and date of culling, ²as the number of inseminations completed before culling.

after haemorrhagic virus vaccination than the maternal A line (Belloumi *et al.*, 2020). This haematological profile contributes to a greater ability to confront infectious challenges and to confer animals a more robust nature (Ferrian *et al.*, 2013).

In France, INRA has developed three divergent selection experiments for longevity, resistance to digestive disorders and weight at birth within litter size. In the first experiment, the objective was to assess the feasibility of selecting for functional longevity, defined as an ability to delay involuntary culling. Functional longevity was measured as the total number of artificial inseminations performed after the first kindling (Larzul *et al.*, 2014). After one generation of selection, the lines differed by 0.75 inseminations over an observation period of 8 artificial inseminations. The number of litters per female was higher in the high longevity line than the low longevity line. Because of this difference between the lines, the total numbers born alive and weaned per female were higher in the high line. Nevertheless, reproductive performance was similar between lines at the 2nd generation (Garreau *et al.*, 2017). In this experiment, the high longevity line accreted more body reserves at the onset of reproductive life than the low line and thereafter maintained higher body reserves until third delivery.

The second divergent selection experiment is focused on improving the resistance to enteropathies and digestive disorders. A binary score based on the signs of enteropathy observed during the growing period was the selection criterion. The resistance animals showed similar mortality and growth rate to those of sensitivity animals, but cumulative mortality was lower in resistant than sensitive animals, when animals were inoculated with an enteropathogenic *E. coli* 0103 strain (Garreau *et al.*, 2012).

When the selection criterion of the lines is to increase or reduce the variability around an optimum, a canalising selection is applied. This is the criterion used for within-litter standard deviation of birth weight (Garreau *et al.*, 2008a; Bodin *et al.*, 2010a). The model assumes that environmental variability of residual variance is also partially controlled by genes. This heteroscedastic model was developed by San Cristobal-Gaudy *et al.* (1998). The within-litter birth weight standard deviations were 7.34 g in the Homogenous line and 11.26 g in the heterogeneous line after 10 generations of selection (Bodin *et al.*, 2010b). Moreover, the homogeneous line showed higher litter size at weaning and lower mortality at birth and at weaning than heterogeneous line. There was no correlated response for the individual weight at birth or the standard deviation and individual weight at weaning (Garreau *et al.*, 2008a). A higher homogeneity in weight birth within litter was related to higher length and capacity of the uterine horn, thus the divergence between the lines could be at least partly due to the characteristics of the reproductive tract (Bolet *et al.*, 2007).

A divergent selection experiment for environmental sensitivity is being carried out at the Miguel Hernández University in Elche (Spain). The selection was based on environmental variance of litter size at birth. This is the first experiment in which selection has been directly performed on environmental variance, treating it as an observed trait. Selection has been successful after 10 generations. The heterogeneous line showed a greater variability of litter size (4.4 kits²) than the homogeneous line (2.7 kits², Blasco *et al.*, 2017). The lines differed in the inflammatory response and the corticotropic response to stress, which were two important components of physiological adaptation to environmental challenges such as infections, suggesting that the homogeneous line was more resilient (Argente *et al.*, 2019; Beloumi *et al.*, 2020). Moreover, a correlated response in the plasma fatty acids profile that modulated the immune cell function was observed (Agea *et al.*, 2020b). Homogeneous line

Table 5: Genetic correlations (standard errors) between disease resistance traits and production traits.

Health trait	ADG ¹ before weaning	Weaning weight		ADG during the fattening period	Live weight at the end of the fattening period		Carcass Yield	Number of kits born alive	Authors
		Direct	maternal		direct	Maternal			
Incidence of bacterial infection									Eady <i>et al.</i> 2004
									-0,13
Extent of abscess dissemination (pasteurellosis)	-0,95 (0.46)								Shrestha <i>et al.</i> , 2019
Extent of bacteria dissemination (pasteurellosis)	-0,62 (0.43)								Shrestha <i>et al.</i> , 2019
Resistance to pasteurellosis score	0,79 (0.36)								Shrestha <i>et al.</i> , 2019
Non-specific mortality				-0.37 (0.08) to -0.34 (0.08)					Ragab <i>et al.</i> , 2015
Morbidity and mortality from ERE ²				-0.35 (0.06) to -0.29 (0.09)					Ragab <i>et al.</i> , 2015
Respiratory syndromes				-0.18 (0.12) to 0.02 (0.06)					Ragab <i>et al.</i> , 2015
Poor body condition score				-0.31 (0.09) to -0.29 (0.06)					Ragab <i>et al.</i> , 2015
Digestive disorders					0.11 (0.07)	-0.11 (0.06)	-0.40 (0.07)		Gunia <i>et al.</i> , 2015
Respiratory disorders					0.01 (0.06)	-0.06 (0.06)	-0.10 (0.08)		Gunia <i>et al.</i> , 2015
Infectious disease					0.06 (0.07)	-0.25 (0.06)	-0.35 (0.08)	-0.08 (0.14) to -0.06 (0.16)	Gunia <i>et al.</i> , 2015, 2018

¹Average Daily Gain. ²Epizootic Rabbit Enteropathy.

showed higher body reserves at delivery and lactation, so the line would be able to better deal with situations of high energy demand than heterogeneous line (García *et al.*, 2018; Agea *et al.*, 2020a). These results agree with the lower mortality at delivery of the does, lower percentage of litter mortality at birth and at weaning, and higher homogeneity of litter weight at weaning found in the homogeneous line (Argente *et al.*, 2019; Agea *et al.*, 2019). Therefore, decreasing litter size variability can favour the dam's survival in the farm.

Furthermore, selection for homogeneity does not seem to reduce litter size, as the Homogeneous line resulted in larger litter size than the heterogeneous line in all generations (Blasco *et al.*, 2017). Studies concerning litter size components have determined that the lines had a similar ovulation rate, but at 48 h after mating, the embryos of the homogeneous line were more developed than in the heterogeneous line and at 72 h also had greater survival (García *et al.*, 2016; Calle *et al.*, 2017). Thus, when a laparoscopy was performed at 12 days of gestation, the number of implanted embryos was higher in the homogeneous line than in the heterogeneous line (Argente *et al.*, 2017).

In summary, selection programmes for longevity, resistance to diseases and birth weight or litter size variability using complex models or simple observations seem to be feasible. Considering that improving the health of breeding rabbits is becoming a crucial issue due to the decreasing antibiotic use in farms, these programmes could have a great impact on the improvement of animal welfare and disease resistance (Gunia *et al.*, 2018). However, the biological mechanisms underlying environmental sensitivity are not yet fully understood. Recently, gut microbiota has become a key regulator of immunity. So, studies using multi-omics approaches are needed to unravel the mechanisms in play.

MULTI-OMICS APPROACH TO STUDY RESISTANCE/SUSCEPTIBILITY TO DISEASES

Sensitivity to most diseases is caused by a complex combination of genomic, biological and environment factors (Mangino *et al.*, 2017). Therefore, a multi-omics approach can help us gain in-depth knowledge about the host immune genes and the role of the microbiome in expression of the host genes to resistance/susceptibility to diseases. This knowledge could be applied in breeding programmes, contributing to the improvement of disease resistance in commercial rabbit lines.

Genomics

Over the past few years, transcriptomics technologies have helped us characterise a large number of functional genes involved in the innate immune response. Transcriptome studies in rabbits after exposure to virus and bacteria have shown upregulation of the major histocompatibility complex (MHC or RLA) class II genes (e.g., *HLA-DMA*, *HLA-DQB2*, *HLA-DRA*, *RLA-DMB*, *RLA-DRB1*, *SLA-DQD1*), and those encoding cytokines/chemokines/chemokine receptors (*IL-1 α* , *IL-1 β* , *IL-2*, *IL-4*, *IL-6*, *IL-8*, *IL-10*, *IL-12*, *IL-17*, *IL-18*, *IL-36*, *IL-37*, *TNF α* , *TRAF3*, *IFN α* , *IFN- β* , *IFI44*, *IFIT5*, *CCL4*, *CCL20*, *CXCL10*, *CXCL11* and *CCR3*), toll-like receptors/interferon regulation factors (e.g., *TLR3*, *TLR4*, *TLR6*, *TLR10*, *IRF7* and *IRF9*), immunoglobulins (e.g., 15 subclasses for IgA), T-cell activation (e.g., *CD2*, *CD4*, *CD27*, *CD28*, *CD74*, *CD80*, *CD86*, and *CTLA4*), oxidative stress and apoptosis (e.g., *COX-2* and *iNOS*) (Schnup and Sansonetti, 2012; Subbian *et al.*, 2013; Jacquier *et al.*, 2015; Uddin *et al.*, 2015; Hou *et al.*, 2016; Suen *et al.*, 2016; Schwensow *et al.*, 2017; Neave *et al.*, 2018; Pinheiro *et al.*, 2018). Recently, a genome-wide association (GWAS) study was performed in the two lines selected divergently for environmental variance of litter size. In that study, Casto-Rebollo *et al.* (2021a) identified 65 genes related to the immune response, 5 to the stress response, and 50 to energy, carbohydrate and lipid metabolism; among those, the genes of *C3orf20*, *GRN*, *EPCAM*, *ENSOCUG00000017494*, *ENSOCUG00000024926*, *ENSOCUG00000026560*, *MYLK*, *HECA*, and *NMNAT3* are highlighted, as they are fixed in both lines. These findings agree with different sensitivity to infections and stress conditions between the homogeneous and heterogeneous lines for environmental variance of litter size (Argente *et al.*, 2019; Beloumi *et al.*, 2020), corroborating the immune system's decisive role in modulation of the animal's resilience.

Microbiomics

The gut microbiota has a pivotal responsibility in susceptibility to diseases and to stress conditions in the host (review by Pickard *et al.*, 2017; review by Kraimi *et al.*, 2019). In this regard, studies with germ-free animals have provided clear evidence that gut microbiota composition plays an essential role in full intestinal blood vessel development, in promoting development of B and T cells in Peyer's Patches of gut-associated lymphoid tissue (GALT), and in driving production of mucosal Ig (review by Martin *et al.*, 2010). Breakthroughs in high-throughput sequencing technology in recent years have made it possible to investigate the rabbit microbiota composition throughout the digestive tract (Massip *et al.*, 2012; Bäuerl *et al.*, 2014; Zhu *et al.*, 2015; Arrazuria *et al.*, 2016; Combes *et al.*, 2017; Crowley *et al.*, 2017; Arrazuria *et al.*, 2018; Jin *et al.*, 2018; Velasco-Galilea *et al.*, 2018; Mattioli *et al.*, 2019; North *et al.*, 2019; Read *et al.*, 2019; Beaumont *et al.*, 2020; Paës *et al.*, 2020; Cotozzolo *et al.*, 2021). In accordance with the different functions in each section of the digestive tract, microbial community composition is different. For example, the stomach and small intestine show a similar composition, Firmicutes being the most abundant phylum (~48%), followed by Bacteroidetes (~18%), Proteobacteria (~22%), and Actinobacteria (~5%). Meanwhile, in the distal segment of the digestive tract (*sacculus rotundus*, caecum and vermiform appendix), Firmicutes doubles its presence (~76%), whereas Bacteroidetes (~12%), Proteobacteria (~2%) and Actinobacteria (~1%) are reduced (see Table 6). Bibliography has reported that factors such as age, sex, food composition and texture, feed intake levels and drinking water temperature can remodel the composition of the gut microbiota (Combes *et al.*, 2013, 2017; Zhu *et al.*, 2015; Jin *et al.*, 2018; Wu *et al.*, 2018; Mattioli *et al.*, 2019; North *et al.*, 2019; Read *et al.*, 2019; Wang *et al.*, 2019a; Beaumont *et al.*, 2020; Paës *et al.*, 2020; Cotozzolo *et al.*, 2021).

The gut microbiota synthesises and releases a large number of metabolites to gut lumen and epithelial surface, such as short-chain fatty acids (SCFAs), mainly acetate, propionate and butyrate, folic acid, indole and indole derivatives, polyamines, histamine, retinoic acid, secondary bile acids, taurine and tryptophan metabolites, which stimulate development of the host immune system (review by Wang *et al.*, 2019b in humans; Table 7). Few studies in rabbits have examined the relationship between the microbiota composition and the production of SCFAs (review by Combes *et al.*, 2013; Jin *et al.*, 2018; Wang *et al.*, 2019a; Wu *et al.*, 2018), and between the microbiota composition and the immune gene expression in intestinal mucosa (Bäuerl *et al.*, 2014; Wang *et al.*, 2019a). These studies have identified a positive correlation between some members of the families Bifidobacterium, Ruminococcaceae and Coprococcus and concentration of butyric acid. Beaumont *et al.* (2020) noted that butyric acid might be involved in gut barrier maturation through the upregulation of genes associated with intestinal absorption (*ALPI*, *CA2* and *MCT1*), transcytosis of the immunoglobulin A (*PIGR*), and antibacterial activity (*CCL20*, *GPX2* and *NOS2*). Regarding relationships between the gut microbiota and immune genes, Bäuerl *et al.* (2014) found in caecum a large association between the families Verrucomicrobiaceae, Enterobacteriaceae and Bacteroidaceae, with expression of genes coding for pro-inflammatory cytokines such as IL-8, IL-6 and TNF- α , although association was low with the Lachnospiraceae and Ruminococcaceae families. Likewise, Wang *et al.* (2019a) reported negative correlations between several members of Ruminococcaceae and Coprococcus and expression of genes coding for pro-inflammatory cytokines such as TGF-1 β and IL-1 β , and positive correlation between Ruminococcaceae and expression of gene coding for anti-inflammatory cytokines such as IL-10.

It is important to note that all studies in rabbit gut microbiota to date have been based on the use of 16S rRNA sequencing. However, this technique has several limitations that metagenomics tries to resolve, such as how to provide a higher taxonomic resolution at the level of species and strain, and to reveal the entire gene repertoire of the community. In order to figure out the effect of the microbiota on host immune gene expression and its susceptibility to diseases, a metagenomic study is being performed on the divergent selection experiment for litter size environmental variance by the UMH team. A preliminary analysis with PLS-DA has allowed us to separate the two divergent lines according to the microbial genes (Belloumi *et al.*, 2021b) and the gut microbiota metabolites (Casto-Rebollo *et al.*, 2021b). From all relevant metabolites identified, the glycerophosphoglycerol, N6-acetyllysine, behenoylcarnitine, ethyl beta-glucopyranoside and equol had the largest contribution to the classification between rabbit lines. These metabolites are involved in the metabolism of xenobiotics, amino acids and lipids. However, further studies are needed to understand the role of these metabolites and the bacteria that produce them. This

Table 7: Effects of microbiota metabolites on host immune function (extracted from Wang *et al.*, 2019b).

Metabolite	Molecular mechanisms	Effects on immune function
Folic acid	Increased expression of the antiapoptotic factor BCL-2	Promotes activation of regulatory T cells
Histamine	Activation of H1R and H2R	Regulates Th1 and Th2 polarisation Inhibits expression of pro-inflammatory cytokines and the MAPK pathway
Indole and indole derivatives	Activation of AhR	Promotes production of IL-22 Production of antimicrobial peptides
Polyamines	Inhibition of pro-inflammatory cytokines expression	Increases production of occludin, zonula occludens 1 and E-cadherin
Retinoic acid	Activation of RAR and RXR heterodimer	Activates the TGF β -SMAD pathway
Secondary bile acids	Activation of GPBAR1 and FXR	Inhibits NF- κ B
Short-chain fatty acids (acetate, propionate, butyrate)	Activation of GPR41 and GPR43	Promotes production of IL-10 Promotes chemotaxis Suppresses activation of NF- κ B and expression of NO Regulates production of ROS
	Inhibition of histone deacetylase	Enhances oxidative phosphorylation, glycolysis and fatty acid synthesis. Promotes antibody production
	Activation of NLRP3 inflammasome (butyrate only)	Promotes production of IL-18
	Binding to the transporter Slc5a8 (propionate and butyrate only)	Inhibits expression of pro-inflammatory cytokines (TNF- α , IL-12 and IFN- γ) and promote production of anti-inflammatory cytokines (IL-10)
Taurine	Activation of the NLRP6 inflammasome	Promotes production of IL-18
Tryptophan metabolites	Activation of GPR35, GPR109A and AhR	Promotes activation of regulatory T cells

BCL-2: B-cell lymphoma 2. H1R: Histamine H1 Receptor. H2R: Histamine H2 Receptor. Th1: T helper 1 lymphocytes. Th2: T helper 2 lymphocytes. MAPK: Mitogen-activated protein kinases. IL: Interleukin. AhR: Aryl hydrocarbon receptor. RAR: Retinoid acid receptor. RXR: Retinoid X receptor. TGF- β : Transforming growth factor- β . GPBAR1: G-Protein Coupled Bile Acid Receptor 1. FXR: *Farnesoid X receptor*. NF- κ B: Nuclear factor kappa-light-chain-enhancer of activated B cells. GPR41: G-Protein Coupled Receptor 41, also called free fatty acid receptor 3 or FFAR3. GPR43: G-Protein Coupled Receptor 43, also called free fatty acid receptor 2 or FFAR2. NO: Nitric oxide. ROS: Reactive oxygen species. NLRP3: NLR Family Pyrin Domain Containing 3. TNF- α : tumour necrosis factor. IFN- γ : Interferon gamma. NLRP6: NLR Family Pyrin Domain Containing 6. GPR35: G-Protein Coupled Receptor 35. GPR109A: G-Protein Coupled Receptor 109A, also called Hydroxycarboxylic Acid Receptor 2 or HCAR2.

study can help us better understand how the selection for litter size environmental variance can modify the gut microbiota and the mechanisms underlying the microbial role in regulation of host resilience.

CONCLUSIONS

Selection programmes based on longevity, resistance to diseases or variability of weight at birth and litter size has been carried out successfully, without decreasing the production traits. Moreover, multi-omics studies are being carried out to gain in-depth knowledge of the host immune genes and the microbiome's role in expression of the host genes for resistance/susceptibility to diseases. This knowledge could be used in breeding programmes, contributing to improving the response to selection for disease resistance in commercial rabbit lines.

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REFERENCES

- Agea I., García M.L., Blasco A., Argente M.J. 2019. Litter survival differences between divergently selected lines for environmental sensitivity in rabbits. *Animals*, 9: 603. <https://doi.org/10.3390/ani9090603>
- Agea I., García M.L., Blasco A., Massányi P., Capcarová M., Argente M.-J. 2020a. Correlated response to selection for litter size residual variability in rabbits' body condition. *Animals*. 10: 2447. <https://doi.org/10.3390/ani10122447>
- Agea I., Muelas R., García M.L., Hernández P., Santacreu M.A., Armero E., Blasco A., Argente M.J. 2020b. Correlated response in plasma fatty acids profile in rabbits selected for environmental sensitivity. In *Proc. 12th World Rabbit Congress*, 1-3 July, 2020. Nantes, France.
- Argente M.J., Calle E.W., García M.L., Blasco A. 2017. Correlated response in litter size components in rabbits selected for litter size variability. *J. Anim. Breed. Genet.*, 134: 505-511. <https://doi.org/10.1111/jbg.12283>
- Argente M.J., García M.L., Zbyňovská K., Petruška P., Capcarová M., Blasco A. 2019. Correlated response to selection for litter size environmental variability in rabbits' resilience. *Animal*, 13: 2348-2355. <https://doi.org/10.1017/S1751731119000302>
- Arrazuría R., Elguezabal N., Juste R. A., Derakhshani H., Khafipour E. 2016. *Mycobacterium avium* Subspecies *paratuberculosis* Infection Modifies Gut Microbiota under Different Dietary Conditions in a Rabbit Model. *Front. Microbiol.*, 7: 446. <https://doi.org/10.3389/fmicb.2016.00446>
- Arrazuría R., Pérez V., Molina E., Juste R.A., Khafipour E., Elguezabal N. 2018. Diet induced changes in the microbiota and cell composition of rabbit gut associated lymphoid tissue (GALT). *Sci. Rep.*, 8: 141031. <https://doi.org/10.1038/s41598-018-32484-1>
- Baselga M., Deltoro J., Camacho J., Blasco A. 1988. Genetic analysis on lung injury in four strains of meat rabbit. In: *Proc. 4th World Rabbit Congress*, 10-14 October, 1988. Budapest, Hungary, Vol. 1, 120-127.
- Baselga M. 2004. Genetic improvement of meat rabbits. Programmes and diffusion. In *Proc. 8th World Rabbit Congress*, 7-10 September, 2004. Puebla, México, Vol. 1, 1-13.
- Bäuerl C., Collado M.C., Zúñiga M., Blas E., Pérez Martínez G. 2014. Changes in cecal microbiota and mucosal gene expression revealed new aspects of epizootic rabbit enteropathy. *PLoS one*, 9: e105707. <https://doi.org/10.1371/journal.pone.0105707>
- Beaumont M., Paës C., Mussard E., Knudsen C., Cauquil L., Aymard P., Barilly C., Gabinaud B., Zemb O., Fourre S., Gautier R., Lencina C., Eutamène H., Theodorou V., Canlet C., Combes S. 2020. Gut microbiota derived metabolites contribute to intestinal barrier maturation at the suckling-to-weaning transition. *Gut Microbes*, 11: 1268-1286. <https://doi.org/10.1080/19490976.2020.1747335>
- Beloumi D., Blasco A., Muelas R., Santacreu M.A., García M.L., Argente M.J. 2020. Inflammatory correlated response in two lines of rabbit selected divergently for litter size environmental variability. *Animals*, 10: 1540. <https://doi.org/10.3390/ani10091540>
- Belloumi D., Argente M.J., García M.L., Blasco A.1, Santacreu M.A. 2021a. Study of biomarkers of disease sensitivity in a robust and standard maternal line. In *Proc. 12th World Rabbit Congress*, 1-3 July, 2020. Nantes, France.
- Belloumi D., Casto-Rebollo C., Blasco A., García M.L., Ibañez-Escriche N., Argente M.J. 2021b. Análisis Metagenómico de la microbiota cecal en dos líneas de conejo seleccionadas divergentemente por varianza ambiental del tamaño de camada. *XIX Jornadas de Producción Animal*, 1-2 June, 2021. Zaragoza, Spain.
- Berghof T.V.L., Poppe M., Mulder H.A. 2019. Opportunities to improve resilience in animal breeding programs. *Front. Genet.* 9: 692. <https://doi.org/10.3389/fgene.2018.00692>
- Blasco A., Martínez-Álvaro M., García M.L., Ibañez-Escriche N., Argente M.J. 2017. Selection for genetic environmental sensitivity of litter size in rabbits. *Genet. Sel. Evol.*, 49: 48-55. <https://doi.org/10.1186/s12711-017-0323-4>
- Bodin L., Bolet G., García M., Garreau H., Larzul C., David I. 2010a. Robustesse et canalisation: vision de généticiens. *INRA Prod. Anim.*, 23: 11-22. <https://doi.org/10.20870/productions-animales.2010.23.1.3281>
- Bodin L., Garcia M., Saleil G., Bolet G., Garreau H. 2010b. Results of 10 generations of canalising selection for rabbit birth weight. In *Proc. 9th World Congress on Genetics Applied to Livestock Production*, August, Leipzig, Germany, 0391.
- Bolet G., Garreau H., Joly T., Theau-Clement M., Falieres J., Hurtaud J., Bodin L. 2007. Genetic homogenisation of birth weight in rabbits: Indirect selection response for uterine horn characteristics. *Livest. Sci.*, 111: 28-32. <https://doi.org/10.1016/j.livsci.2006.11.012>
- Calle E.W., García M.L., Blasco A., Argente M.J. 2017. Correlated response in early embryonic development in rabbits selected for litter size variability. *World Rabbit Sci.*, 25: 323-327. <https://doi.org/10.4995/wrs.2017.6340>
- Casto-Rebollo C., Argente M.J., García M.L., Blasco A., Ibañez-Escriche N. 2021a. Immunological genes selected for environmental variance could control the animal resilience. In *Proc. 12th World Rabbit Congress*, 1-3 July, 2020. Nantes, France.
- Casto-Rebollo C., Argente M.J., García M.L., Blasco A., Ibañez-Escriche N. 2021b. Selection for environmental variance of litter size modified the cecum metabolic profile. *72nd Annual Meeting of European Federation of Animal Science (EAAP)*, August, Davos, Switzerland.
- Cifre P., Baselga M., García-Ximénez F., Vicente J. 1998. Performance of hyperprolific rabbit line. I. Litter size traits. *J. Anim. Breed. Genet.* 115: 131-138. <https://doi.org/10.1111/j.1439-0388.1998.tb00336.x>
- Colditz I.G., Hine B.C. 2016. Resilience in farm animals: biology, management, breeding and implications for animal welfare. *Anim. Prod. Sci.*, 56: 1961-1983. <https://doi.org/10.1071/AN15297>
- Combes S., Fortun-Lamothe L., Cauquil L., Gidenne T. 2013. Engineering the rabbit digestive ecosystem to improve digestive health and efficacy. *Animal*, 7: 1429-1439. <https://doi.org/10.1017/S1751731113001079>

- Combes S., Massip K., Martin O., Furbeyre H., Cauquil L., Pascal G., Bouchez O., Le Floc'h N., Zemb O., Oswald I.P., Gidenne T. 2017. Impact of feed restriction and housing hygiene conditions on specific and inflammatory immune response, the cecal bacterial community and the survival of young rabbits. *Animal*, 11: 854-863. <https://doi.org/10.1017/S1751731116002007>
- Cotozzolo E., Cremonesi P., Curone G., Menchetti L., Riva F., Biscarini F., Marongiu M.L., Castrica M., Castiglioni B., Miraglia D., Luridiana S., Brecchia G. 2021. Characterization of bacterial microbiota composition along the gastrointestinal tract in rabbits. *Animals*, 11: 31. <https://doi.org/10.3390/ani11010031>
- Crowley E.J., King J.M., Wilkinson T., Worgan H.J., Huson K. M., Rose M.T., McEwan N.R. 2017. Comparison of the microbial population in rabbits and guinea pigs by next generation sequencing. *PLoS One*, 12: e0165779. <https://doi.org/10.1371/journal.pone.0165779>
- Eady S.J., Garreau H., Hurtaud J. 2004. Heritability of resistance to bacterial infection in commercial meat rabbit populations. *In Proc. 8th World Rabbit Congress, 7-10 September, 2004. Puebla, Mexico*, 51-56.
- Eady S.J., Garreau H., Gilmour A.R. 2007. Heritability of resistance to bacterial infection in meat rabbits. *Livest. Sci.*, 112: 90-98. <https://doi.org/10.1016/j.livsci.2007.01.158>
- El Nagar, A.G., Sánchez J.P., Ragab, M., Mínguez C., Baselga M. 2020. Genetic variability of functional longevity in five rabbit lines. *Animal*, 14: 1111-1119. <https://doi.org/10.1017/S1751731119003434>
- Ferrian S., Blas E., Larsen T., Sánchez J.P., Friggens N.C., Corpa J.M., Baselga M., Pascual J.J. 2013. Comparison of immune response to lipopolysaccharide of rabbit does selected for litter size at weaning or founded for reproductive longevity. *Res. Vet. Sci.*, 94: 518-525. <https://doi.org/10.1016/j.rvsc.2013.01.008>
- Ferrian S., Guerrero I., Blas E., García-Diego F.J., Viana D., Pascual J.J., Corpa J.M. 2012. How selection for reproduction or foundation for longevity could have affected blood lymphocyte populations of rabbit does under conventional and heat stress conditions. *Vet. Immunol. Immunopathol.*, 150: 53-60. <https://doi.org/10.1016/j.vetimm.2012.08.007>
- Formoso-Rafferty N., Cervantes I., Ibáñez-Escriche N., Gutiérrez J.P. 2016. Correlated genetic trends for production and welfare traits in a mouse population divergently selected for birth weight environmental variability. *Animal*, 10: 1770-1777. <https://doi.org/10.1017/S1751731116000860>
- García M.L., Blasco A., Argente M.J. 2016. Embryologic changes in rabbit lines selected for litter size variability. *Theriogenology*, 86: 1247-1250. <https://doi.org/10.1016/j.theriogenology.2016.04.065>
- García M.L., Blasco A., García M.E., Argente M.J. 2018. Correlated response in body condition and energy mobilisation in rabbits selected for litter size variability. *Animal*, 13: 784-789. <https://doi.org/10.1017/S1751731118002203>
- Garreau H., Larzul C., Ducrocq V. 2001. Analyse de longévité de la souche de lapins INRA 1077. *In Proc. 9^{mes} Journées de la Recherche Cunicole. Paris, France*, 217-220.
- Garreau H., Licois D., Rupp R., Rochambeau, H. de. 2006. Genetic variability of the resistance to epizootic rabbit enteropathy (ERE): new results. *In Proc. 8th World Congress on Genetics Applied to Livestock Production, Belo Horizonte, Brazil*, 15-28.
- Garreau H., Bolet G., Larzul C., Robery-Granié, C., Saleil G., San Cristobal M., Bodin L. 2008a. Results of four generations of a canalising selection for rabbit birth weight. *Livest. Sci.*, 119: 55-62. <https://doi.org/10.1016/j.livsci.2008.02.009>
- Garreau H., Eady S.J., Hurtaud J., Legarra A. 2008b. Genetic parameters of production traits and resistance to digestive disorders in a commercial rabbit population. *In Proc. 9th World Rabbit Congress, 10-13 June, 2008. Verona, Italy, Vol. 1*, 103-107.
- Garreau H., Brard S., Hurtaud J., Guitton E., Cauquil L., Licois D., Schwartz B., Combes S., Gidenne T. 2012. Divergent selection for digestive disorders in two commercial rabbit lines: response of crossbred young rabbits to an experimental inoculation of *Escherichia coli* 0-103. *In Proc. 10th World Rabbit Congress, 3-6 September, 2012. Sharm El-Sheikh, Egypt, Vol. 1*, 153-157.
- Garreau H., Larzul C., Tudela F., Ruesche J., Ducrocq V., Fortun-Lamothe L. 2017. Energy balance and body reserves in rabbit females selected for longevity. *World Rabbit Sci.*, 25: 205-213. <https://doi.org/10.4995/wrs.2017.5216>
- Groen A.F., Steine T., Colleau J.J., Pedersen J., Pribyl J., Reinsch N. 1997. Economic values in dairy cattle breeding, with special reference to functional traits. Report of an EAAP-working group. *Livest. Prod. Sci.*, 49, 1-21. [https://doi.org/10.1016/S0301-6226\(97\)00041-9](https://doi.org/10.1016/S0301-6226(97)00041-9)
- Gunia M., David I., Hurtaud J., Maupin M., Gilbert H., Garreau H. 2015. Resistance to infectious diseases is a heritable trait in rabbits. *J. Anim. Sci.* 93: 5631-5638. <https://doi.org/10.2527/jas.2015-9377>
- Gunia M., David I., Hurtaud J., Maupin M., Gilbert H., Garreau H. 2018. Genetic parameters for resistance to non-specific diseases and production traits measured in challenging and selection environments; application to a rabbit case. *Front. Genet.*, 9: 467. <https://doi.org/10.3389/fgene.2018.00467>
- Hou Y., Zhao D., Liu G., He F., Liu B., Fu S., Hao Y., Zhang W. 2016. Transcriptome analysis of rabbit spleen with hog cholera lapinized virus infection based on high-throughput sequencing technology. *Bing Du Xue Bao.* 32: 316-23.
- Ibáñez-Escriche N., Moreno A., Nieto B., Piqueras P., Salgado C., Gutiérrez J.P. 2008a. Genetic parameters related to environmental variability of weight traits in a selection experiment for weight gain in mice; signs of correlated canalised response. *Genet. Sel. Evol.*, 40: 279-293. <https://doi.org/10.1051/gse:2008003>
- Ibáñez-Escriche N., Varona L., Sorensen D., Noguera J.L. 2008b. A study of heterogeneity of environmental variance for slaughter weight in pigs. *Animal*, 2: 19-26. <https://doi.org/10.1017/S1751731107001000>
- Jacquier V., Estellé J., Schmalz-Panneau B., Lecardonnel J., Moroldo M., Lemonnier G., Turner-Maier J., Duranthon V., Oswald I.P., Gidenne T., Rogel-Gaillard C. 2015. Genome-wide immunity studies in the rabbit: transcriptome variations in peripheral blood mononuclear cells after in vitro stimulation by LPS or PMA-Ionomycin. *BMC Genomics*, 16: 26-44. <https://doi.org/10.1186/s12864-015-1218-9>
- Jin D.X., Zou H.W., Liu S.Q., Wang L.Z., Xue B., Wu D., Tian G., Cai J., Yan T.H., Wang Z.S., Peng Q.H. 2018. The underlying microbial mechanism of epizootic rabbit enteropathy triggered by a low fiber diet. *Sci. Rep.*, 8: 12489. <https://doi.org/10.1038/s41598-018-30178-2>
- Knap P.W. 2005. Breeding robust pigs. *Aust. J. Exp. Agric.*, 45: 763-773. <https://doi.org/10.1071/EA05041>

- Kraimi N., Dawkins M., Gebhardt-Henrich SG., Velge P., Rychlik I., Volf J., Leterrier C. 2019. Influence of the microbiota-gut-brain axis on behavior and welfare in farm animals: A review. *Physiol. Behav.*, 210: 112658. <https://doi.org/10.1016/j.physbeh.2019.112658>
- Larzul C., Gondret F., Combes S., Rochambeau H. de. 2005. Divergent selection on 63 day body weight in the rabbit: response on growth, carcass and muscle traits. *Genet. Sel. Evol.*, 37: 105-122. <https://doi.org/10.1051/gse:2004038>
- Larzul C., Ducrocq V., Tudela F., Juin H., Garreau H. 2014. The length of productive life can be modified through selection: an experimental demonstration in the rabbit. *J. Anim. Sci.*, 92: 2395-2401. <https://doi.org/10.2527/jas.2013-7216>
- Lenoir G., Maupin M., Leloir C., Garreau H. 2013. Analyse de la longévité des lapines d'une lignée commerciale. In *Proc. 15^{èmes} Journées de la Recherche Cunicole. Le Mans, France, 181-184.*
- Lukefahr S.D., Odi H.B., Atakora J.K.A. 1996. Mass selection for 70-day body weight in rabbits. *J. Anim. Sci.*, 74: 1481-1489. <https://doi.org/10.2527/1996.7471481x>
- Mangino M., Roederer M., Beddall M., Nestle K.O., Spector T.D. 2017. Innate and adaptive immune traits are differentially affected by genetic and environmental factors. *Nat. Commun.*, 8: 13850-13858. <https://doi.org/10.1038/ncomms13850>
- Martin R., Nauta A.J., Ben Amor K., Knippels L.M.J., Knol J., Garszen J. 2010. Early Life: Gut microbiota and immune development in infancy. *Benef. Microbes*, 1: 367-382. <https://doi.org/10.3920/BM2010.0027>
- Massip K., Combes S., Cauquil L., Zemb O., Gidenne T. 2012. High throughput 16SDNA sequencing for phylogenetic affiliation of the caecal bacterial community in the rabbit - Impact of the hygiene of housing and of the intake level. In *Proc. Symposium on Gut Microbiology. Gut microbiota: friend or foe? Clermont-Ferrand - Francia, 17-20 June, 2012.*
- Matics Z.S., Nagy I., Gerencsér Z.S., Radnai I., Gyovai P., Donkó T., Dalle Zotte A., Curik I., Szendrő Z.S. 2014. Pannon breeding program in rabbit at Kaposvár University. *World Rabbit Sci.*, 22: 287-300. <https://doi.org/10.4995/wrs.2014.1511>
- Mattioli S., Dal Bosco A., Combes S., Moscati L., Crotti S., Cartoni Mancinelli A., Cotozzolo E., Castellini C. 2019. Dehydrated alfalfa and fresh grass supply in young rabbits: Effect on performance and caecal microbiota biodiversity. *Animals*, 9: 341. <https://doi.org/10.3390/ani9060341>
- Mormede P., Terenina E. 2012. Molecular genetics of the adrenocortical axis and breeding for robustness. *Domest. Anim. Endocrinol.*, 43: 116-131. <https://doi.org/10.1016/j.domaniend.2012.05.002>
- Mulder H., Hill W., Vereijken A., Veerkamp R. 2009. Estimation of genetic variation in residual variance in female and male broiler chickens. *Animal*, 3: 1673-1680. <https://doi.org/10.1017/S1751731109990668>
- Neave M.J., Hall R.N., Huang N., McColl K.A., Kerr P., Hoehn M., Taylor J., Strive T. 2018. Robust innate immunity of young rabbits mediates resistance to rabbit hemorrhagic disease caused by *Lagovirus Europaeus* Gl.1 But Not Gl.2. *Viruses*, 10: 512-534. <https://doi.org/10.3390/v10090512>
- Nielsen H., Amer P. 2007. An approach to derive economic weights in breeding objectives using partial profile choice experiments. *Animal*, 1: 1254-1262. <https://doi.org/10.1017/S1751731107000729>
- North M.K., Dalle Zotte, A., Hoffman, L.C. 2019. Composition of rabbit caecal microbiota and the effects of dietary quercetin supplementation and sex thereupon. *World Rabbit Sci.*, 27: 185-198. <https://doi.org/10.4995/wrs.2019.11905>
- Paës C., Gidenne T., Bébin K., Duperray J., Gohier C., Guéné-Grand E., Rebours G., Bouchez O., Barilly C., Aymard P., Combes S. 2020. Early introduction of solid feeds: Ingestion level matters more than prebiotic supplementation for shaping gut microbiota. *Front. Vet. Sci.*, 7: 261. <https://doi.org/10.3389/fvets.2020.00261>
- Pickard J.M., Zeng M.Y., Caruso R., Núñez G. 2017. Gut microbiota: Role in pathogen colonization, immune responses, and inflammatory disease. *Immunol. Rev.*, 279: 70-89. <https://doi.org/10.1111/immr.12567>
- Piles M., Blasco A. 2003. Response to selection for growth rate in rabbits. *World Rabbit Sci.*, 11: 53-62. <https://doi.org/10.4995/wrs.2003.497>
- Piles M., Garreau H., Rafel O., Larzul C., Ramon J., Ducrocq V. 2006. Survival analysis in two lines selected for reproductive traits. *J. Anim. Sci.*, 84: 1658-1665. <https://doi.org/10.2527/jas.2005-678>
- Piles M., Baselga M., Sánchez J.P. 2014. Expected response to different strategies of selection to increase heat tolerance assessed by changes in litter size in rabbit. *J. Anim. Sci.*, 92: 4306-4312. <https://doi.org/10.2527/jas.2014-7616>
- Piles M., Sánchez J.P. 2019. Use of group records of feed intake to select for feed efficiency in rabbit. *J. Anim. Breed. Genet.*, 136: 474-483. <https://doi.org/10.1111/jbg.12395>
- Pinheiro A., de Sousa-Pereira P., Strive T., Knight K.L., Woof J.M., Esteves P.J., Abrantes J. 2018. Identification of a new European rabbit IgA with a serine-rich hinge region. *PLoS ONE*, 13: e0201567. <https://doi.org/10.1371/journal.pone.0201567>
- Ragab M., Ramon J., Rafel O., Quintanilla R., Piles M., Sanchez J.P. 2015. Paramètres génétiques des phénotypes liés aux maladies chez le lapin en engraissement nourri avec deux régimes alimentaires différents. In *Proc. 16^{ème} Journées de la Recherche Cunicole. Le Mans, France. 69-72.*
- Read T., Fortun-Lamothe L., Pascal G., Boulch M.L., Cauquil L., Gabinaud B., Bannelier C., Balmisse E., Destombes N., Bouchez O., Gidenne T., Combes S. 2019. Diversity and co-occurrence pattern analysis of caecal microbiota establishment at the onset of solid feeding in young rabbits. *Front. Microbiol.* 10: 973. <https://doi.org/10.3389/fmicb.2019.00973>
- Reiss J., Bridle J.R., Montoya J.M., Woodward G. 2009. Emerging horizons in biodiversity and ecosystem functioning research. *Trends Ecol. Evol.*, 24: 505-514. <https://doi.org/10.1016/j.tree.2009.03.018>
- Rochambeau H., de la Fuente L.F., Rouvier R., Ouhayoun J. 1989. Sélection sur la vitesse de croissance post-sevrage chez le lapin. *Genet. Sel. Evol.*, 21: 527-546. <https://doi.org/10.1186/1297-9686-21-4-527>
- Sánchez J.P., Baselga M., Peiró R., Silvestre M.A. 2004. Analysis of factors influencing longevity of rabbit does. *Livest. Prod. Sci.* 90: 227-234. <https://doi.org/10.1016/j.livprodsci.2004.06.002>
- Sánchez J.P., Baselga M., Ducrocq V. 2006. Genetic and environmental correlations between longevity and litter size in rabbits. *J. Anim. Breed. Genet.*, 123: 180-185. <https://doi.org/10.1111/j.1439-0388.2006.00590.x>
- Sánchez J.P., Theilgaard P., Mínguez C., Baselga M. 2008. Constitution and evolution of a long-lived productive rabbit line. *J. Anim. Sci.*, 86: 515-525. <https://doi.org/10.2527/jas.2007-0217>
- San Cristobal-Gaudy M., Elsen J.M., Bodin L., Chevalet C. 1998. Prediction of the response to a selection for canalization of a continuous trait in animal breeding. *Genet. Sel. Evol.*, 30: 423-451. <https://doi.org/10.1186/1297-9686-30-5-423>

- Sauvant D., Martin O. 2010. Robustesse, rusticité, flexibilité, plasticité... les nouveaux critères de qualité des animaux et des systèmes d'élevage: définitions systémique et biologique des différents concepts. *INRA Prod. Anim.*, 23: 5-10. <https://doi.org/10.20870/productions-animales.2010.23.1.3280>
- Savietto D., Cervera C., Blas E., Baselga M., Larsen T., Friggens N.C., Pascual J.J. 2013. Environmental sensitivity differs between rabbit lines selected for reproductive intensity and longevity. *Animal*, 7: 1969-1977. <https://doi.org/10.1017/S175173111300178X>
- Savietto D., Friggens N., Pascual J.J. 2015. Reproductive robustness differs between generalist and specialist maternal rabbit lines: the role of acquisition and allocation of resources. *Genet. Sel. Evol.*, 47: 2. <https://doi.org/10.1186/s12711-014-0073-5>
- Shrestha M., Garreau H., Balmisse E., Bed'hom B., David I., Fadeau A., Guitten E., Helloin E., Lenoir G., Maupin M., Robert R., Lantier F., Gunia M. 2018. Estimation of Genetic Parameters of Pasteurellosis Resistance in Crossbred Rabbits. In *Proc. 11th World Congress on Genetics Applied to Livestock Production*. Auckland, New-Zealand.
- Shrestha M., Garreau H., Balmisse E., Bed'hom B., David I., Guitten E., Lenoir G., Maupin M., Robert R., Lantier F., Gunia M. 2019. Projet RELAPA (génomique pour la Résistance génétique des LAPins à la Pasteurellose): paramètres génétiques. In *Proc. 18^{èmes} Journées de la Recherche Cunicole*. Nantes, France. 77-80.
- Schwensow N.I., Detering H., Pederson S., Mazzoni C., Sinclair R., Peacock D., Kovaliski J., Cooke B., Fickel J., Sommer S. 2017. Resistance to RHD virus in wild Australian rabbits: Comparison of susceptible and resistant individuals using a genome wide approach. *Mol. Ecol.*, 26: 4551-4561. <https://doi.org/10.1111/mec.14228>
- Schnup P., Sansonetti P.J. 2012. Quantitative RT-PCR profiling of the rabbit immune response: assessment of acute *Shigella flexneri* infection. *PLoS One*, 7: e36446. <https://doi.org/10.1371/journal.pone.0036446>
- Sobey W.R. 1969. Selection for resistance to myxomatosis in domestic rabbits (*Oryctolagus cuniculus*). *J. Hygiene*, 67: 743-754. <https://doi.org/10.1017/s0022172400042194>
- Star L., Ellen E.D., Uitdehaag K., Brom F.W.A. 2008. A plea to implement robustness into a breeding goal: poultry as an example. *J. Agric. Environ. Ethics*, 21: 109-125. <https://doi.org/10.1007/s10806-007-9072-7>
- Subbian S., O'Brien P., Kushner N.L., Yang G., Tsenova L., Peixoto B., Bandyopadhyay N., Bader J.S., Karakousis P.C., Fallows D., Kaplan G. 2013. Molecular immunologic correlates of spontaneous latency in a rabbit model of pulmonary tuberculosis. *Cell Commun Signal.*, 11: 16. <https://doi.org/10.1186/1478-811X-11-16>
- Suen W.W., Uddin M.J., Prow N.A., Bowen R.A., Hall R.A., Bielefeldt-Ohmann H. 2016. Tissue-specific transcription profile of cytokine and chemokine genes associated with flavivirus control and non-lethal neuropathogenesis in rabbits. *Virology*, 494: 1-14. <https://doi.org/10.1016/j.virol.2016.03.026>
- Theilgaard P., Sánchez J.P., Pascual J.J., Berg P., Friggens N.C., Baselga M. 2007. Late reproductive senescence in a rabbit line hyper selected for reproductive longevity, and its association with body reserves. *Genet. Sel. Evol.*, 39: 207-223. <https://doi.org/10.1051/gse:2006043>
- Theilgaard P., Baselga M., Blas M., Friggens N.C., Cervera C., Pascual J.J. 2009. Differences in productive robustness in rabbits selected for reproductive longevity or litter size. *Animal*, 3: 637-646. <https://doi.org/10.1017/S1751731109003838>
- Uddin M.J., Suen W.W., Prow N.A., Hall R.A., Bielefeldt-Ohmann H. 2015. West Nile virus challenge alters the transcription profiles of innate immune genes in rabbit peripheral blood mononuclear cells. *Front. Vet. Sci.*, 14: 76. <https://doi.org/10.3389/fvets.2015.00076>
- Velasco-Galilea M., Piles M., Viñas M., Rafel O., González-Rodríguez O., Guivernau M., Sánchez J.P. 2018. Rabbit microbiota changes throughout the intestinal tract. *Front Microbiol*, 9: 2144. <https://doi.org/10.3389/fmicb.2018.02144>
- Wang Q., Fue W., Guo Y., Tang Y., Du H., Wang M., Liu A., Li Q., An L., Tian J., Li M., Wu, Z. 2019a. Drinking warm water improves growth performance and optimizes the gut microbiota in early postweaning rabbits during winter. *Animals*, 9: 34. <https://doi.org/10.3390/ani9060346>
- Wang G., Huang S., Wang Y., Cai S., Yu H., Liu H., Zeng X., Zhang G., Qiao S. 2019b. Bridging intestinal immunity and gut microbiota by metabolites. *Cell Mol Life Sci.*, 76: 3917-3937. <https://doi.org/10.1007/s00018-019-03190-6>
- Wu Z., Zhou H., Li F., Zhang N., Zhu Y. 2018. Effect of dietary fiber levels on bacterial composition with age in the cecum of meat rabbits. *Microbiologyopen*, 8: e00708. <https://doi.org/10.1002/mbo3.708>
- Youssef Y.M.K., Khalil M.H., Afifi E.A., El-Raffa A.M.E., Zaheds M. 2000. Heritability and non-genetic factors for lifetime production traits in New Zealand White rabbits raised in intensive system of production. In *Proc. 7th World Rabbit Congress*. 4-7 July, 2000. Valencia, Spain. 497-503.
- Zhu Y., Wang C., Li F. 2015. Impact of dietary fiber/starch ratio in shaping caecal microbiota in rabbits. *Can. J. Microbiol.*, 61: 771-784. <https://doi.org/10.1139/cjm-2015-0201>
- Ziadi C., Mocé M.L., Laborda P., Blasco A., Santacreu M.A. 2013. Genetic selection for ovulation rate and litter in rabbits: Estimation of genetic parameters and direct and correlated response. *J. Anim. Sci.*, 91: 3113-3120. <https://doi.org/10.2527/jas.2012-6043>
- Zomeño C., Hernández P., Blasco A. 2013. Divergent selection for intramuscular fat content in rabbits. I. Direct response to selection. *J. Anim. Sci.*, 91: 4526-4531. <https://doi.org/10.2527/jas.2013-6361>