Genetic factors of functional traits

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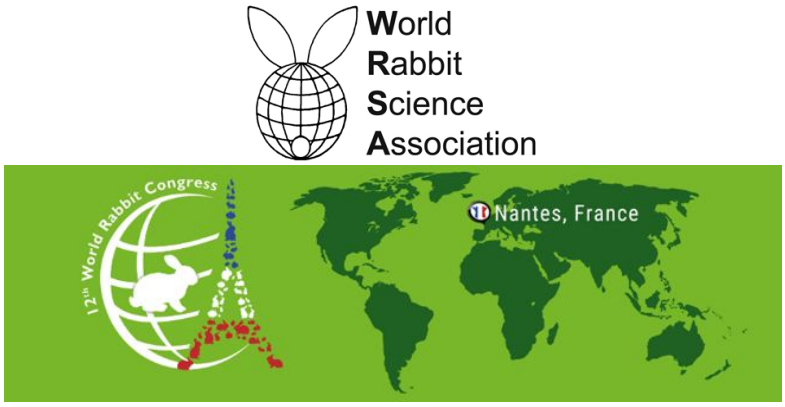

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GENETIC FACTORS OF FUNCTIONAL TRAITS

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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, and 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 obtained. Genomics studies have revealed associations in regions related to immune system functionality and stress in lines selected for litter size variability. Knowledge of gut microbiota role on the rabbit's immune response is very limited. A multi-omics approach can help to know microbial mechanisms on regulation immunity genes of the host.

Keywords: Genetic, longevity, omics, resilience, resistance to diseases, selection.

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 summarized those characters of an animal that increase efficiency by reduced costs of input. 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 a high production potential and a 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 (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, diseases 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 if disease resistance were heritable started 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 3). Heritability of the resistance traits varies from 0.02 to 0.64 depending on the disease, its prevalence and the model used (Table 4). 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.

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 *et al.*,2000
Number of AI[2]	0.10	Weibull	France	INRA 1077	Garreau *et al.*, 2001
Number of AI[2]	0.05	Discrete model	France	INRA 1077	Garreau *et al.*, 2001
Length of lifetime[3]	0.05	Cox model	Spain	V line	Sánchez *et al.*, 2004
Length of lifetime[4]	0.10	Cox model	Spain	V line	Sánchez *et al.*, 2006
Length of lifetime[3]	0.16 to 0.24	Cox model	Spain	Prat	Piles *et al.*, 2006
Number of AI[2]	0.17 to 0.19	Discrete model	France	INRA 1077	Piles *et al.*, 2006
Number of AI[2]	0.12	Discrete model	France	Hycole line D	Lenoir *et al.*, 2013
Functional longevity[5]	0.07	Cox model	Spain	A line	El Nagar *et al*., 2020
Functional longevity[5]	0.03	Cox model	Spain	V line	El Nagar *et al*., 2020
Functional longevity[5]	0.14	Cox model	Spain	H line	El Nagar *et al*., 2020
Functional longevity[5]	0.05	Cox model	Spain	LP line	El Nagar *et al*., 2020
Functional longevity[5]	0.02	Cox model	Spain	R line	El Nagar *et al*., 2020

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

Table 2: 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 *et al.*, 2006[1]
Number of kits born alive	-0.72	Lenoir *et al.*, 2013[2]
Number of kits at weaning	-0.17 (0.11)	Sánchez *et al*., 2006
Litter weight at weaning	-0.7	Lenoir *et al*., 2013
Teat number	-0.39	Lenoir *et al*., 2013
Adult weight	-0.2	Lenoir *et al*., 2013

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

Table 3: 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 *et al.*, 2008a, Bodin *et al.*, 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 *et al.*, 2017

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

The genetic correlations between the mean and the variability for birth weight and litter size were no different from zero (Table 3). Genetic correlations between resistance to diseases and production traits are either favourable or not 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.

Table 4: Heritability (standard errors) for disease resistance traits[1]

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
	Survival to myxomatosis	0-1		0.36				
Respiratory infection caused by *Pasteurella multocida* and *Bordetella bronchiseptica*	Extension of lesions on lung lobes	0-5	0.07 (0.03) to 0.18 (0.09)		Spain	A,V, R,B	maternal and paternal	Baselga *et al.*, 1988
	Average score of lung lobe lesions	0-5	0.12 (0.05) to 0.28 (0.14)					
Bacterial infection caused by *Pasteurella multocida* or *Staphylococcus aureus*	Incidence of infection	0-1	0.03 (0.01) to 0.04 (0.01)	0.13 (0.04) to 0.38 (0.11)	France	2 commercial populations	paternal	Eady *et al.* 2004
	Weekly 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 *et al.*, 2007
	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 *et al.*, 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 *et al.*, 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 *et al.*, 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 *et al.*, 2008b. Gunia *et al.*, 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)					

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

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					-0,13				Eady *et al.* 2004
Extent of abscess dissemination (pasteurellosis)	-0,95 (0.46)								Shrestha *et al.*, 2019
Extent of bacteria dissemination (pasteurellosis)	-0,62 (0.43)								Shrestha *et al.*, 2019
Resistance to pasteurellosis score	0,79 (0.36)								Shrestha *et al.*, 2019
Non-specific mortality				-0.37 (0.08) to -0.34 (0.08)					Ragab *et al.*, 2015
Morbidity and mortality from ERE[2]				-0.35 (0.06) to -0.29 (0.09)					Ragab *et al.*, 2015
Respiratory syndromes				-0.18 (0.12) to 0.02 (0.06)					Ragab *et al.*, 2015
Poor body condition score				-0.31 (0.09) to -0.29 (0.06)					Ragab *et al.*, 2015
Digestive disorders					0.11 (0.07)	-0.11 (0.06)	-0.40 (0.07)		Gunia *et al.*, 2015
Respiratory disorders					0.01 (0.06)	-0.06 (0.06)	-0.10 (0.08)		Gunia *et al.*, 2015
Infectious disease		-0.34 (0.12) to 0.05 (0.14)	-0.06 (0.20) to -0.04 (0.22)		0.06 (0.07)	-0.25 (0.06)	-0.35 (0.08)	-0.08 (0.14) to -0.06 (0.16)	Gunia *et al.*, 2015, 2018

[1]Average Daily Gain. [2]Epizootic Rabbit Enteropathy

SELECTION PROGRAMMES AND RESPONSE TO SELECTION

The first approach to selection for disease resistance was a programme of mass selection 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 weeks 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 has been 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 a.*, 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 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 observed signs of enteropathy 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 sensitivity 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 their 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 kits^2) than the Homogeneous line (2.7 kits^2, 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 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 Homogenous 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 hours after mating, the embryos of the Homogeneous line were more developed than in the Heterogeneous line and at 72 hours 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 programs of longevity, resistance to diseases and birth weight or litter size variability using complex models or simple observations seem to be feasible. Taking into account 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 to characterize a large number of functional genes involving in the innate immune response. Transcriptome studies in rabbits after exposition to virus and bacteria have showed the up-regulation 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-1α, IL-1β, IL-2, IL-4, IL-6, IL-8, IL-10, IL-12, IL-17, IL-18, IL-36, IL-37, TNFα, TRAF3, IFNα, 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*), and oxidative stress and apoptosis (e.g., *COX-2 and iNOS*) (Hou *et al.*, 2016; Jacquier *et al.*, 2015; Neave *et al.*, 2018; Pinheiro *et al.*, 2018; Schnup and Sansonetti, 2012, Schwensow *et al.*, 2017; Subbian *et al.*, 2013; Suen *et al.*, 2016; Uddin *et al.*, 2015). Recently a genome-wide association (GWAS) study has performed in the two lines selected divergently for environmental variance of litter size. Casto-Rebollo *et al.* (2021a) identified in this study 65 genes related to the immune response, 5 to the stress response, and 50 to energy, carbohydrate and lipid metabolism; among those highlight the genes of C3orf20, GRN, EPCAM, ENSOCUG00000017494, ENSOCUG00000024926, ENSOCUG00000026560, MYLK, HECA, and NMNAT3 because they are fixed in both lines. These findings agree with different sensitivity to infections and stress conditions between the homogeneous and the 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 (Arrazuria *et al.*, 2016; Arrazuria *et al.*, 2018; Bäuerl *et al.*, 2014; Beaumont *et al.*, 2020; Combes *et al.*, 2017; Cotozzolo *et al.*, 2021; Crowley *et al.*, 2017; Jin *et al.*, 2018; Mattioli *et al.*, 2019; Massip *et al.*, 2012; Paës *et al.*, 2020; North *et al.*, 2019; Read *et al.*, 2019; Velasco-Galilea *et al.*, 2018; Zhu *et al.*, 2015). 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 (Beaumont *et al.,* 2020; Combes *et al.,* 2013 and 2017; Cotozzolo *et al.,* 2021; Jin *et al.,* 2018; Paës *et al.,* 2020; Mattioli *et al.,* 2019; Read *et al.,* 2019; North *et al.,* 2019; Wang *et al.,* 2019a; Wu *et al.,* 2018; Zhu *et al.,* 2015).

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 the gut barrier maturation through the up-regulation of genes associated with the intestinal absorption (*ALPI, CA2* and *MCT1*), the transcytosis of the immunoglobulin A (*PIGR*), and the 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, but association was low with families Lachnospiraceae and Ruminococcaceae. 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-1β and IL-1β, 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 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 xenobiotics, amino acids and lipids metabolisms. However, further studies are needed to understand the role of these metabolites and the bacteria that produce them. This 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.

Table 6. Average percentages of bacteria phyla in the stomach, small intestine, *sacculus rotundus* (SR) caecum and vermiform appendix content (VA).

	Stomach		Small Intestine		*SR*		Caecum													VA
	Jin *et al.*, 2018a	Cotozzolo et al., 2021b	Jin *et al.*, 2018a	Cotozzolo et al., 2021b	Arrazuria *et al.*, 2018c	Massip *et al.*, 2012d	Bäuerl *et al.*, 2014e	Zhu *et al.*, 2015f	Arrazuria *et al.*, 2016g	Combes *et al.*, 2017h	Crowley *et al.*, 2017i	Velasco-Galilea *et al.*, 2018j	Jin *et al.*, 2018a	Mattioli *et al.*, 2019k	North *et al.*, 2019l	Read *et al.*, 2019m	Beaumont *et al.*, 2020n	Paës *et al.*, 2020o	Cotozzolo *et al.*, 2021b	Arrazuria *et al.*, 2018c
Firmicutes	44.6	68	41.7	40.5	87.1	90	78.3	77.0	71.0	83	53	76.5	72.1	78.9	72.0	91	60	89	43	87.0
Bacteroidetes	18.9	16	32.3	1.5	2.10	4.6	15.7	7.9	13.7	5.8	42	7.46	13.2	14.1	9.82	6	30	9	40	1.63
Proteobacteria	27.5		18.3		0.83	0.7		1.4	0.16	0.58	3.74	1.61	5.09	3.02	11.1		2	1		0.40
Tenericutes					1.42		2.39	<1	0.43		0.15	7.48		3.02	1.4	1.67	5	0.3		1.18
Actinobacteria	5.10	2	4.05	11	0.81	0.9			0.39	0.37	0.79	0.73	2.81	0.85	3.62			0.5	0	0.78
Cyanobacteria		1		0.5	1.25				4.23			0.87							0	1.35
Verrucomicrobia		5		3			2.40	7.9				1.81			1.28				15	
Euryarchaeota		6		30.5								0.06							1	
Saccharibacteria					3.39				0.16											3.85
Spirochaetae								<1						0.09						
Patescibacteria		3		13.5															1	
Epsilonbacteraeota																	1	0.2		
Unknown					3.10				9.89			3.43								3.79

a: Samples taken at 55 days. b: samples taken at 110 days. c: Samples taken at 39 weeks. d: Samples taken at 63 days. e: Samples taken at 40 days. f: Samples taken at 82 days. g: Samples taken at 36 weeks. h: Samples taken at 64 days. i: No specific data obtained in wild animal. j: Samples taken at 66 days. k: Samples taken at 45 days. l: Samples taken at 13 weeks. m: Samples taken at 49 days. n: Samples taken at 30 days. o: Samples taken at 57 days.

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 TGFβ–SMAD pathway
. Secondary bile acids	Activation of GPBAR1 and FXR	Inhibits NF-κB
. Short-chain fatty acids (acetate, propionate, butyrate)	Activation of GPR41 and GPR43	Promotes production of IL-10 Promotes chemotaxis Suppresses activation of NF-κB 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: Linfocitos T helper 1. Th2: Linfocitos T helper 2. 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-κB: 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: tumor 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.

CONCLUSIONS

Selection programs 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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GENETIC FACTORS OF FUNCTIONAL TRAITS

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GENETIC FACTORS OF FUNCTIONAL TRAITS

—INTRODUCTION

—GENETIC CONTROL

—SELECTION PROGRAMS AND RESPONSE TO SELECTION

—MULTI-OMICS APPROACH TO STUDY RESISTANCE/SUSCEPTIBILITY TO DISEASES

—CONCLUSIONS

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INTRODUCTION

- PRIORITIES IN RABBIT BREEDING
  1. ANIMAL WELFARE
  2. DISEASE RESISTANCE
  3. REDUCE ANTIBIOTICS
  4. PRODUCTIVITY

- CONCEPTS:
  1. ROBUSTNESS
  2. RUSTICTY
  3. PLASTICITY
  4. RESILIENCE

- TRAITS MEASURED:
  1. LONGEVITY
  2. HEALTH INDICATORS
  3. ENVIRONMENTAL VARIANCE

OBJECTIVE

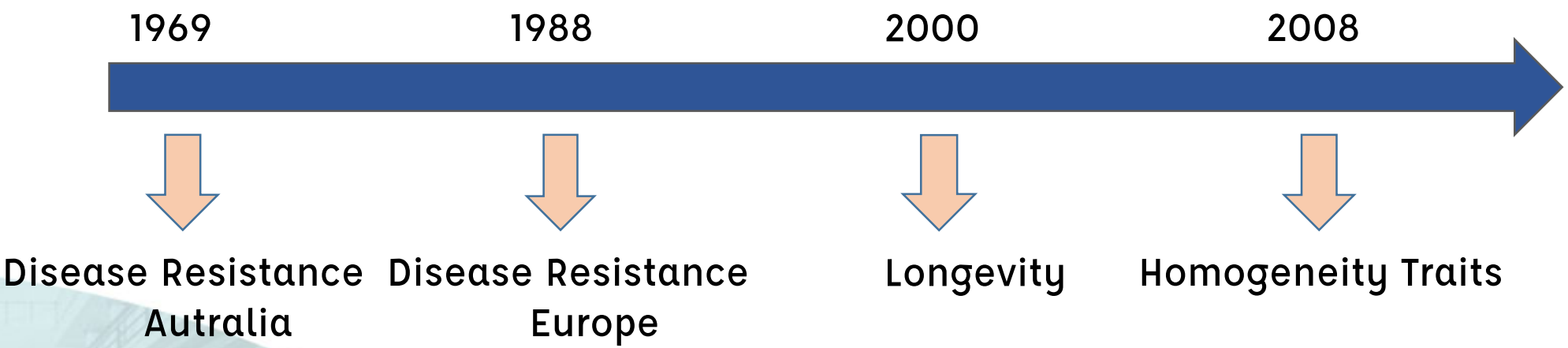
The objectives of this review are:

—to discuss the genetic control of longevity, diseases resistance traits and variability of birth weight and litter size.

—presenting the selection programmes with inclusion of these traits

—describing the first results from a multi-omics analysis of resistance/susceptibility to diseases

GENETIC CONTROL



GENETIC CONTROL

DISEASE RESISTANCE TRAITS

LONGEVITY

HOMOGENETIY TRAITS

- ✓ Main diseases:
  - ✓ Pasteurellosis
  - ✓ Myxomatosis
  - ✓ Epizootic rabbit enteropathy
- ✓ Traits description:
  - ✓ Survival/Mortality
  - ✓ Lesions
  - ✓ Abcess
  - ✓ Abnormal growth
  - ✓ Poor body condtion

h^2 = 0.02-0.64
Average (0.11)

Genetic correlations:
. Growth traits: <0
. Litter size, weight at weaning: = 0

GENETIC CONTROL

DISEASE RESISTANCE TRAITS

LONGEVITY

HOMOGENETIY TRAITS

Length of lifetime	• Date of the first presentation to a male and the date of death or culling	h^2 = 0.05-0.24
Number of AI	• Total number of artificial inseminations performed after the first kindling or death	h^2 = 0.05-0.19
Functional longevity	• Difference between the date of the first positive palpation test and the date of death or culling due to involuntary causes	h^2 = 0.02-0.14

GENETIC CONTROL

DISEASE RESISTANCE TRAITS

LONGEVITY

HOMOGENETIY TRAITS

Genetic correlations < 0

Number of born alive: 0.16; -0.72	At weaning: . Litter size: -0.17 Litter weight: -0.7
Number of teats: -0.39	Adult weight: -0.2

Pseudo-genetic correlations

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GENETIC CONTROL

DISEASE RESISTANCE TRAITS

LONGEVITY

HOMOGENETIY TRAITS

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

TRAIT	VARIABILITY	MEAN
BIRTH WEIGHT	0.01	0.09
		0.06
LITTER SIZE	0.08	- 0.06
		0.10

SELECTION PROGRAMMES AND RESPONSE TO SELECTION

SELECTION PROGRAMMES:

AUTRALIA	POLITECHNIC UNIVERSITY OF VALENCIA	INRA	MIGUEL HERNÁNDEZ UNIVERSITY
Resistance to myxomatois	Longevity	Divergent selection: Longevity Resistance to digestive disorders Weight at birth within litter size	Divergent selection: Litter size variability

SELECTION PROGRAMMES AND RESPONSE TO SELECTION

AUTRALIA

Resistance to myxomatosis

- ✓ Mass selection
- ✓ Rabbits were infected with 4 virus strains
- ✓ Percentage of recovery increased from 50 to 80% for the least virulent strain and from 10 to 20% for the most virulent virus strain

SELECTION PROGRAMMES AND RESPONSE TO SELECTION

POLITECHNIC UNIVERSITY OF VALENCIA

Longevity (LP)

- ✓ Line was founded by applying high selection intensity:
  - ✓ Females: between 25 and 41 parities
  - ✓ prolificacy ranged from 7.5 to 11.9 young born alive
- ✓ Selection criterium: litter size at weaning

LP line vs V line

- ✓ LP line was 1.3 time less likely to leave the herd than the V line
- ✓ ≠ Body condition

LP line vs A line

- ✓ ≠ Haematological profile: leukocytes populations

SELECTION PROGRAMMES AND RESPONSE TO SELECTION

INRA

Divergent Selection

Functional Longevity

- ✓ Selection criterium: Functional longevity
- ✓ After 1 generation:
  - ✓ Lines differ 0.75 inseminations
- ✓ After 2 generations:
  - ✓ Reproductive performance was similar between lines
  - ✓ More body reserves in the High longevity line.

SELECTION PROGRAMMES AND RESPONSE TO SELECTION

INRA

Divergent Selection

Resistance to digestive disorders

- ✓ Selection criterion: Binary score based on the observed signs of enterophaty during growing period
- ✓ Similar mortality and growth rate in both lines.
- ✓ Cumulative mortality was lower in resistant than sensitivity line, when animals were inoculated with *E. Coli* 0103 strain.

SELECTION PROGRAMMES AND RESPONSE TO SELECTION

INRA

Divergent Selection

Weight at birth within litter size

- ✓ Model of San Cristobal-Gaudi *et al* (1998)
- ✓ Criterion of selection: within litter standard deviation of birth weight

SELECTION PROGRAMMES AND RESPONSE TO SELECTION

INRA

Divergent Selection

Weight at birth within litter size

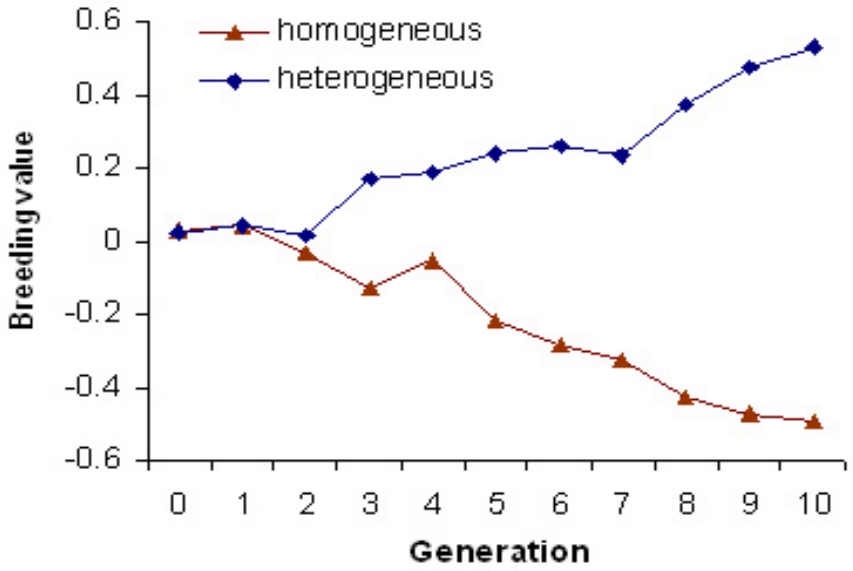


Figure. Genetic trends for birth weight variability (Bodin et al., 2010)

- ✓ Direct response to selection: 1.7% per generation of litter weight standard deviation
- ✓ Correlated response:
  - ✓ Higher litter size at weaning in Homogenous line
  - ✓ Lower mortality at birth and at weaning in Homogenous line

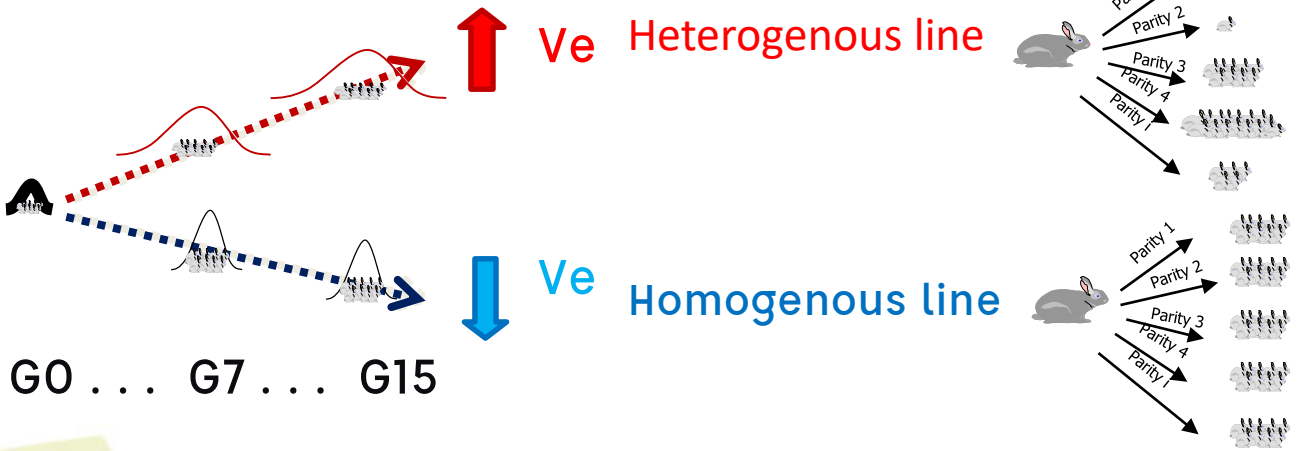
SELECTION PROGRAMMES AND RESPONSE TO SELECTION

SIX SELECTION PROGRAMMES:

MIGUEL HERNÁNDEZ UNIVERSITY

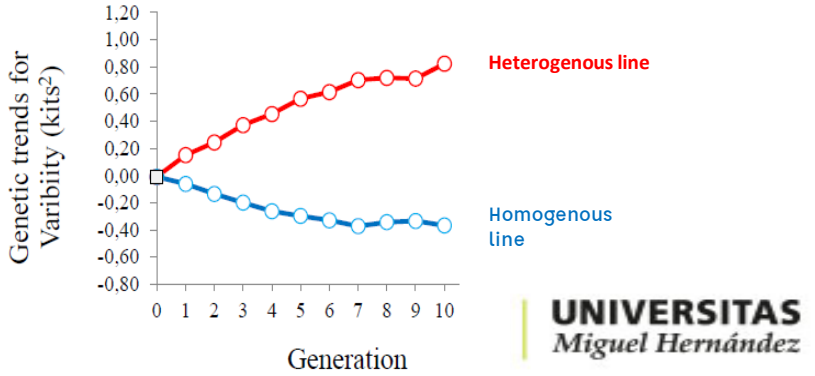
- Divergent Selection
- Litter size variability

✓ Criterion of selection: environmental variance of litter size at birth (Ve)



✓ After 10 generations:

✓ Direct response to selection:



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SELECTION PROGRAMMES AND RESPONSE TO SELECTION

SIX SELECTION PROGRAMMES:

MIGUEL HERNÁNDEZ UNIVERSITY

- Divergent Selection
- Litter size variability

- ✓ Correlated response (I):
  - ✓ Homogenous line showed.....
    - Lower sensitivity to stress and diseases,
    - Higher body reserves at delivery and lactation,
    - Lower mortality at delivery of the does,
    - 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

SELECTION PROGRAMMES AND RESPONSE TO SELECTION

SELECTION PROGRAMMES:

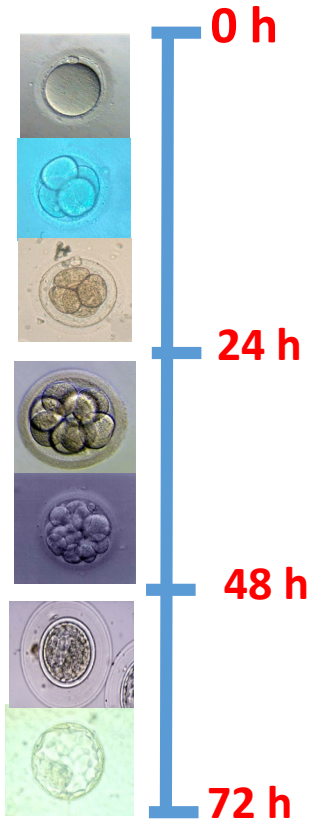
MIGUEL HERNÁNDEZ UNIVERSITY

- Divergent Selection
- Litter size variability

✓ Correlated response (II):

✓ Homogenous line showed.....

- No difference in ovulation rate
- Higher embryo development from 48 h p.c.
- Higher number of implanted embryos at 12 d of gestation
- Higher litter size at birth



MULTI-OMICS APPROACH TO STUDY ENVIRONMENTAL SENSITIVITY

MIGUEL HERNÁNDEZ UNIVERSITY

Divergent Selection

Litter size variability

✓ Genomics

✓ Candidate genes:

○ Immune response	65
○ Stress response	5
○ Energy, carbohydrate and lipid metabolism	50
○ Reproduction and embryo development	29

Among those highlight the genes :

TTC23L
FBXL20
GHDC
ENSOCUG00000031631
SLC18A1
CD300LG
ENSOCUG00000006264
MC2R

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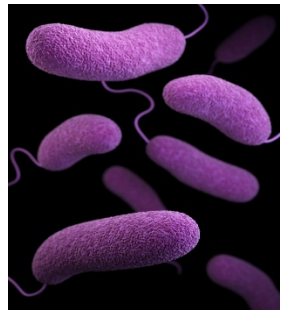
SELECTION PROGRAMMES AND RESPONSE TO SELECTION

SIX SELECTION PROGRAMMES:

MIGUEL HERNÁNDEZ UNIVERSITY

- Divergent Selection
- Litter size variability



- ✓ *Gut Microbiota (GI)*
  - Two divergent lines separated according to 48 bacteria, 294 microbial genes, and 29 microbiota metabolites
  - *Highlighting,* 3 especie bacteria (*Limosilactobacillus fermentum*, *Alistipes shahii* y *Acetatifactor muris),* 13 genes and 7 metabolites involved in phenylalanine, tyrosine and tryptophan metabolism
  - These metabolites suggest that selection for VE modified GI

CONCLUSIONS

- ✓ Selection programs for longevity, resistance to diseases and birth weight or litter size variability have been successful.

- ✓ Knowledge of gut microbiota in these lines can help to design probiotics for increasing resistance to illness.

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THANKS FOR YOUR ATTENTION