World Rabbit Sci. 2018, 26: 287-298
doi:10.4995/wrs.2018.7644

ANALYSIS OF THE IMPACT OF CYTOPLASMIC AND MITOCHONDRIAL INHERITANCE ON LITTER SIZE AND CARCASS IN RABBITS

NGUYEN N.T.*, BRAJKOVIC V.†, CUBRIC-CURIK V.†, RISTOV S.‡, VEIR Z.§, SZENDRŐ Z.*, NAGY I.*, CURIK I.†

*Kaposvár University, Faculty of Animal Science, Guba S. 40, 7400 Kaposvár, Hungary.
†Univeristy of Zagreb, Svetošimunska 25, 10000 Zagreb, Croatia.
‡Ruđer Bošković Institute, Bijenička cesta 54, 10000 Zagreb, Croatia .
§University of J.J. Strossmayer, Faculty of Medicine, Kralja Petra Svačića 1d, 31000 Osijek, Croatia.

Abstract: The effects of mitogenome variation on economically important traits have been reported in a number of domestic animal species. In this study, the first of its kind on rabbits, we have performed the estimation of the contribution of cytoplasmic and D-loop mitochondrial DNA (mtDNA) sequence effects on the litter size and carcass traits in three Pannon rabbit breeds (Pannon Ka, Pannon Large and Pannon White). The observed effects of both estimates, coming from cytoplasmic or D-loop mtDNA variation, were negligible. The most likely explanation for the results obtained is the lack of mitogenome polymorphism in all three populations, as suggested from the analysis performed on the D-loop mtDNA sequence, here assigned to the two most frequent rabbit haplotypes. The extent of potential benefits of the introduction, or alteration, of mitogenome variation in rabbit breeding remains an open question for future research.

Key Words: mitochondrial DNA, breeding value, litter size, carcass, rabbit.

INTRODUCTION

Understanding the relationship between DNA sequence and economically important production traits is one of the major challenges in modern animal breeding. The efficiency of breeding programmes is based on an accurate estimation of genetic parameters such as heritability, genetic correlation and breeding value. Quantitative traits are generally assumed to be under the control of infinitely linked or unlinked genes, each of infinitesimal additive effects, and with a considerable influence of non-genetic (environmental) components (Hill, 2010).

On the other hand, other genetic factors such as mitogenome variation can also influence inheritance of quantitative traits and consequently have an impact on the estimation of the genetic parameters. The mitochondrial genome (mitogenome) is a closed circular DNA molecule. In rabbits, the length of the molecule is approximately 17245 nucleotides, varying by repeated motifs placed in the control region, encoding for the synthesis of 13 proteins essential for the oxidative phosphorylation system and responsible for regulation of the cellular energy metabolism (Wallace, 1999). Mitogenome is inherited only through the maternal lineage, thus providing a genetic mechanism for cytoplasmic inheritance with a potential impact on the quantitative traits and the estimation of genetic parameters important in animal breeding (Van Vleck, 2000).

In a simulation study, Boettcher *et al.* (1996c) observed that ignoring cytoplasmic effects will lead to biased estimates of heritability. Starting with the study of Bell *et al.* (1985), the cytoplasmic effects were most comprehensively covered in cattle populations, analysed as the effects of maternal lineages present in individuals (cows) on milk production (Kennedy 1986; Boettcher *et al.,* 1996b; Boettcher *et al.,* 1997), as well as on the growth traits (Pun *et al.,* 2012). The estimated effects in all those studies varied from negligible to the impact of up to 5% of phenotypic variation (Gibson

Correspondence: I. Nagy., nagy.istvan@ke.hu. Received *May 2017* - Accepted *September 2018.*
https://doi.org/10.4995/wrs.2018.7644

et al., 1997). Similar models were also performed in poultry (Szwaczkowski *et al.,* 1999) and sheep (Hanford *et al.,* 2003; Snowder *et al.,* 2004). In all those studies, cytoplasmic effects were analysed under assumption that maternal lineages derived from the pedigree reflect the actual mitogenome polymorphism. However, this is quite a relaxed assumption and, in order to obtain more accurate estimates, quantitative cytoplasmic genetic models have to be further extended to the association analyses of the mitogenome variation (polymorphism), from D-loop mitochondrial DNA (mtDNA) to complete mitogenome, with production traits. Good examples are provided in studies related to cattle (Boettcher *et al.,* 1996a; Mezzadra *et al.,* 2005), poultry (Li *et al.,* 1998; Zhao *et al.,* 2015), swine (Yen *et al.,* 2007; Fernández *et al.,* 2008; Yu *et al.,* 2015, Tsai *et al.,* 2016) and sheep (Chen *et al.,* 2017) populations, as well as to humans (Ruiz-Pesini *et al.,* 2000; Liu *et al.,* 2012), where the association of certain mitogenome polymorphisms with quantitative traits have been analysed.

To date, no single analysis has evaluated the impact of the cytoplasmic effects, either of maternal lineages or of mitogenome sequence variation, on any traits that are important in rabbit production. Thus, the main objective of this paper was to estimate the effects of cytoplasmic and mitochondrial inheritance on litter size traits such as the number of kits born alive (NBA), number of kits born dead (NBD) and the total number of kits born (TNB) in Pannon Ka (PK), Pannon Large (PL) and Pannon White (PW) rabbit breeds, as well as on a carcass trait: the thigh muscle volume (TMV) measured in vivo by computer tomography (CT), but only in PW.

MATERIAL AND METHODS

Data information

Data in this study was collected in 3 Pannon breeds; PW (established in 1992), PK (established in 1999) and PL (established in 2004) over a period of 24 yr (1992 to 2016) at the experimental rabbit farm of the Kaposvár University. General development and management of the Pannon rabbit breeds was described by Matics *et al.* (2014). In Table 1 we present the kindling records, the size of the pedigree, and the number of does and mating bucks included in the analysis. The litter size traits analysed were the number of kits born alive (NBA), number of kits born dead (NBD) and the total number of kits born (TNB). Thigh muscle volume (TMV cm^3) was obtained by summing the surface of 11-12 CT scans (Nagy *et al.,* 2013a). Due to the fact that records showed highly unbalanced frequencies for litter kindling, parities were combined into 4 categories (parities 1, 2, 3-10, >10). Descriptive statistics of the examined traits are also presented in Table 1.

Pedigree and molecular analyses

Sampling for molecular analysis

Prior to molecular analyses, the authors performed a pedigree analysis (defining) maternal lineage in order to avoid examining a lot of animals with the same female founder. To determine maternal (founder) lineages from the pedigree

Table 1: Descriptive statistics for the litter size and carcass traits analyses in Pannon rabbit breeds.

Breed	Trait	Animals in pedigree	Does	Bucks	Records	Mean	SD	Range
Pannon	NBA	7832	2941	1241	20227	8.54	3.04	1-19
White	NBD	7832	2941	1241	20227	0.43	1.10	0-15
	TNB	7832	2941	1241	20227	8.97	3.08	1-19
	TMV	8001	2000	1017	6724	374.50	42.50	230-570
Pannon	NBA	5198	899	1896	13847	9.27	3.12	1-20
Ka	NBD	5198	899	1896	13852	0.43	1.14	0-15
	TNB	5198	899	1896	13847	9.70	3.16	1-21
Pannon	NBA	3714	935	1737	5913	8.69	3.16	1-20
Large	NBD	3714	935	1737	5990	0.82	1.68	0-15
	TNB	3714	935	1737	5988	9.40	3.32	1-21

NBA: number of kits born alive, NBD: number of kits born dead, TNB:s total number of kits born, TMV: thigh muscle volume (cm^3).

and to choose samples for molecular analysis we used *mag_sampl module* implemented in the MaGelLan 1.0 (Maternal Genealogy Lineage Analyser) software (Ristov *et al.* 2016; https://github.com/sristov/magellan). Analysis was performed on the previously corrected pedigree utilising the same software. In total, there were 2, 6 and 4 maternal lineages in PK, PL and PW breeds, respectively. The blood of several rabbits per each maternal lineage was further taken for molecular analyses. In this way, we were able to analyse maternal lineage segregation consistency throughout the pedigree.

Molecular analysis

The DNA was extracted from 31 (27 and 4 from maternal lineages 1-2) PK, 25 (1, 1, 4, 14, 4 and 1 from maternal lineages 1-6) PL and 22 (2, 1, 12 and 7 from maternal lineages) PW blood samples using commercially available NucleoSpin Blood Kit according to manufacturer's protocol (Macherey-Nagel GmbH & Co. KG, Germany). A 332-base pairs (bp) fragment of the mitochondrial D-loop region was amplified by polymerase chain reaction (PCR) using forward (5'-CACCATCAGCACCCAAAG-3') (Melo-Ferreira *et al.,* 2009) and reverse primers (5'-ATTTAAGAGGAACGTGTGGG-3') (Pierpaoli *et al.,* 1999). PCRs were performed in a 25 µL volume containing 0.2 µM of each primer and using Emerald AMP GT PCR Master Mix (Takara Bio Inc, Japan) according to the manufacturer's protocol. The amplification reactions were performed on a iCycler (Biorad, Germany), comprised of an initial denaturation at 95°C for five min, 38 cycles of denaturation at 95°C for 45 s, annealing at 52°C for 45 s, extension at 72°C for 1 min and final extension at 72°C for 1 min. After purifying the first round of PCR products, PCR was performed again using the Big Dye-terminator method in a thermal cycler. This PCR products/sequences was then read (sequenced) using a capillary electrophoresis ABI PRISM® 3100-Avant Genetic Analyzer. The sequences were visualised and aligned using MEGA 7 (Kumar *et al.,* 2016), together with sequences taken from the GeneBank. Haplotypes were constructed using DNA Sp 5.10 (Librado and Rozas, 2009) and Median-joining network (Bandelt *et al.,* 1999) was constructed by PopART (Leigh and Bryant, 2015). D-loop mtDNA sequences of Pannon rabbits were deposited in GenBank under the accession numbers KY977609-KY977686. A detailed description of all sequences used in analyses is provided in Supplement Table S1 (available at the end of the document).

Maternal pedigree verification (Maternal lineage segregation pedigree consistency)

Originally, only 2 haplotypes (D-loop mtDNA sequences), hereafter named H1 and H2, were found in PL and PW, while only H1 was found in PK population. We further imputed (assigned) obtained mtDNA sequences to the maternal lineages (*Mag_stat* module from MaGelLan) and consequently verified the consistency of maternal lineage segregation through the pedigree (*Mag_verif* module from MaGelLan). A single conflict was found in PL pedigree, where H2, present in individual 13-20188 (YOB 2013), was not consistent with the pedigree of three sequenced individuals in the same maternal lineage. After the identification, the utilisation of *Mag_con_demo* module as described in Čačić *et al.,* (2014), and the exclusion of non-consistent individual from the dataset, only H1 was present in the PL breed. Thus, the difference between two haplotypes (H1 *vs.* H2) for the litter size and carcass traits was tested only in PW breed. The final number of descendants for each lineage and each haplotype (H1 & H2) is shown in Table 2.

Calculation of inbreeding coefficients

Inbreeding coefficient of dams (F_{Dam}) and litters (F_{Litter}) were calculated with ENDOG 4.8 software (Gutiérrez *et al.,* 2010; http://webs.ucm.es/info/prodanim/html/JP_Web.htm#_Endog_3.0:_A). The pedigree files did not contain all

Table 2: The final number of descendants for each lineage and each haplotype.

Breed	PK	PL		PW	
D-loop mt DNA Haplotype	H1	H1	Total	H1	H2
Maternal lineage 1	2429	94	386	0	386
Maternal lineage 2	638	73	258	0	258
Maternal lineage 3	-	227	1078	1078	0
Maternal lineage 4	-	600	440	440	0
Maternal lineage 5	-	238	-	-	-
Maternal lineage 6	-	35	-	-	-
Total numbers	3067	1267	2162	1518	644

PK, Pannon Ka; PL, Pannon Large; PW, and Pannon White.

progeny of the does presented in the data set. Thus, before calculation of litter inbreeding coefficients, the dummy progeny was created according to the unique combinations of their parents (does and related mating bucks) and then litter inbreeding coefficients were calculated.

Quantitative genetic analyses

To analyse the impact of cytoplasmic and D-loop mtDNA effects on the analysed traits, we employed 10 different models, described in detail in Table 3. The first 7 models (see Table 3) referred to the litter size traits. All these models had the same fixed effects known to have impact on their variability (Nagy *et al.,* 2013a, Nagy *et al.,* 2013b). Thus, as a fixed effect we modelled: parity (4), year-month (101 in PL, 246 in PW and 185 in PK), F_{Dam} and F_{Litter}. In the first 7 models, permanent environment and additive genetic effects were treated as random effects while models were different due to the presence/absence of dam or sire or both cytoplasmic or D-loop mtDNA effects, all treated as random effects. Here, in addition to the models with maternal lineage of dam (does) effect, which is a classical approach used in a large number of studies (Boettcher *et al.,* 1996; Boettcher *et al.,* 1997; Snowder *et al.,* 2004), we also modelled the maternal lineage of sire (bucks) effect. This decision was based on the established evidence that certain mitogenome mutations have strong impact on human male fertility (Ruiz-Pesini *et al.,* 2000; John *et al.,* 2005) and, consequently, can affect the litter size. We applied models 5, 6 and 7 to estimate the variance of the contribution of the difference between H1 and H2, applicable only in PW breed. The last three models (see Table 3) referred to the thigh muscle volume and all had the same fixed effects known to have impact on their variability (Gyovai *et al.* 2012). After the same logic, the following fixed effects were modelled in all three models (Table 3): year-month (75), F_{Dam}, body weight at CT-scan (1), sex (2) and Pixel (3). Additive genetic effects and random litter effects were treated as random effects, while three models were extended with D-loop mtDNA effects.

Mathematical description and general structure referred to NBA, NBD and TNB (equation 1) and TMV (equation 2) basic models are:

$$y = Xb + Za + Wp + e \quad (1)$$

$$y = Xb + Za + Wc + e \quad (2)$$

Table 3: Description of models used in estimating cytoplasmic and D-loop mtDNA effects.

Litter size traits models (1-7)	1	2	3	4	5*	6*	7*	8	9	10*
Carcass traits models (8-10)	1	2	3	4	5*	6*	7*	8	9	10*
Fixed effects										
Parity	X	X	X	X	X	X	X			
Year-month	X	X	X	X	X	X	X	X	X	X
F_{Dam}	X	X	X	X	X	X	X	X	X	X
F_{Litter}	X	X	X	X	X	X	X			
Body weight at CT-scan								X	X	X
Sex								X	X	X
Pixel								X	X	X
Random effects										
Permanent	X	X	X	X	X		X			
Additive	X	X	X	X	X		X	X	X	X
Maternal lineages of dames		X		X					X	
Maternal lineages of sires			X	X						
D-loop mtDNA of mothers					X		X			X
D-loop mtDNA of sires						X	X			
Litter								X	X	X

*Reduced dataset as the number of known haplotypes following maternal segregation was smaller. F_{Dam} and F_{Litter} are inbreeding coefficients of dam and litter, respectively.

where y=vector of phenotypic observations, b=vector of fixed effects, a=vector of additive genetic effects, p=vector of permanent environmental effects (random, only considered in equation 1), c=vector of common litter effects (random, only considered in equation 2), e=vector of residuals, while X, Z and W are incidence matrices relating the records to the fixed, animal and random permanent environmental or common litter effects, respectively.

Additionally, the extended models accounted for cytoplasmic effects to NBA, NBD and TNB (equation 3) and TMV (equation 4)

$$y = Xb + Za + Wp + Km + e \quad (3)$$

$$y = Xb + Za + Wc + Km + e \quad (4)$$

where m=vector of random cytoplasmic effects, and K is the incidence matrix relating records to random cytoplasmic effects.

In addition to estimating the variance of the contribution of the difference between H1 and H2 (as in models 5, 6, 7, and 10), we also analysed the significance of the difference between H1 and H2 haplotypes. Conclusions from results obtained were the same as in models 5, 6, 7 and 10, and are not presented.

Variance components and genetic parameters were estimated by REML method using the PEST (for data coding) (Groeneveld, 1990: ftp://ftp.tzv.fal.de/pub/pest/doc/pest-manual-Apr-2006.pdf) and VCE6 software (Groeneveld, *et al.,* 2008; ftp://ftp.tzv.fal.de/pub/vce6/doc/vce6-manual-3.1-A4.pdf) applying the single-trait animal models. In order to compare the fit of the models, the PREDICTION procedure of PEST (Groeneveld, 1990) was applied to calculate mean squared error (MSE), bias and correlation between the observed and predicted values of NBA, NBD, TNB and TMV.

RESULTS

Descriptive statistics

Means and standard deviations of TNB and NBA of the analysed breeds (Table 1) showed the highest value for Pannon Ka breed (maternal line), which was expected as this population is more intensively selected for the litter size traits than are Pannon White or Pannon Large population. However, the observed litter size values were close to those reported previously (Al-Saef *et al.,* 2008; Nagy *et al.,* 2011; Nagy *et al.,* 2013; Nagy *et al.,* 2014). On the other side, PW breed is intensively selected for the lean production (Matics *et al.,* 2014); as a result, TMV might be higher in comparison to the previous studies (Gyovai *et al.,* 2011).

D-loop mtDNA diversity

The variability of D-loop mtDNA polymorphism in 3 Pannon Rabbit breeds was extremely low, as in PK and PL only 1 haplotype (H1) was found, while in PW only 2 haplotypes, H1 (76%) and H2 (24%), were identified. The phylogenetic position of 2 haplotypes (H1 and H2) found in Pannon Rabbits is presented in Figure 1. While separated by 13 mutations, haplotypes H1 and H2 were grouped within 2 most common rabbit haplotypes (see Figure 1). This

Table 4: Estimated variance components (V) and genetic parameters for additive genetic (A), cytoplasmic (cyt), D-loop mtDNA (Hcyt) and environmental effects (E) for thigh muscle volume (in cm^3; TMV) of Pannon White rabbits.

Model	V_A	h^2	V_{cyt}	cyt^2	V_{Hcyt}	$Hcyt^2$	V_C	c^2	V_E	e^2	MSE
8	246.86	0.275	-	-			68.52	0.076	583.19	0.649	419.88
9	247.00	0.275	0.000	0.000			68.54	0.076	583.14	0.649	419.76
10	280.02	0.302			0.000	0.000	55.07	0.059	592.57	0.639	418.05

Model 10 refers to the reduced dataset as the number of known haplotypes following maternal segregation was smaller; V_A, V_{cyt}, V_{Hcyt}, V_c and V_E are additive, cytoplasmic maternal, D-loop mtDNA haplotype, random litter, and residual variances, respectively; h^2 is the narrow sense heritability; cyt^2 is the contribution of cytoplasmic maternal variance to the phenotypic variance; $Hcyt^2$ is the contribution of D-loop mtDNA haplotype variance to the phenotypic variance; c^2 is the contribution of common litter variance to the phenotypic variance; e^2 is the contribution of residual variance to phenotypic variance; MSE is mean squared error.

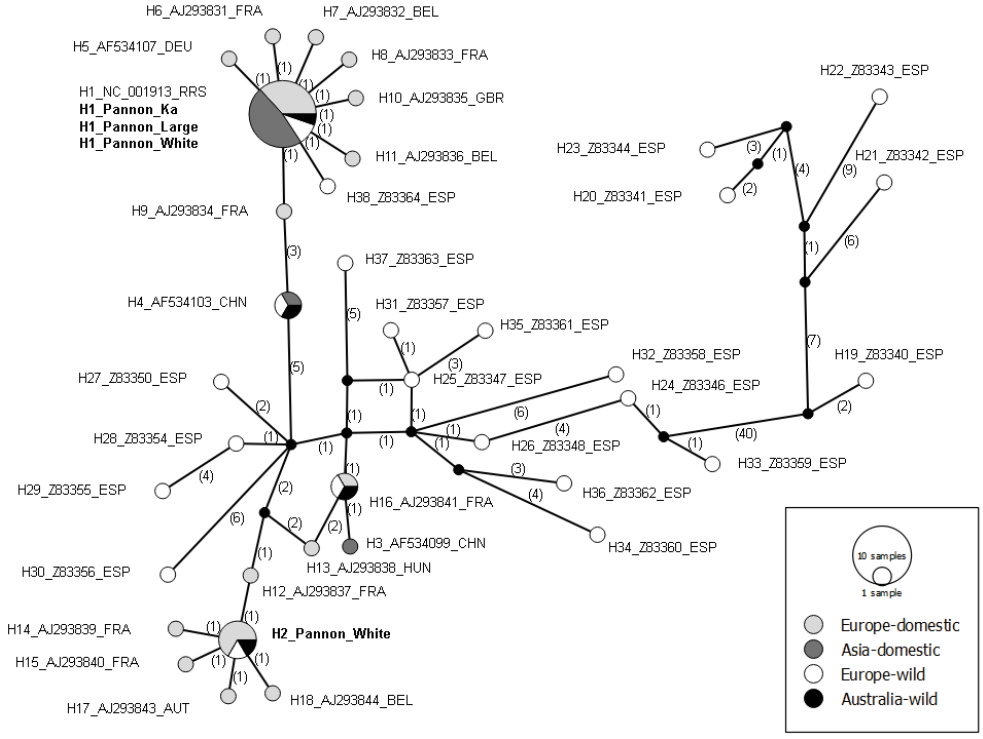

Figure 1: Median-joining network diagram showing phylogenetic positions of haplotypes found in Pannon Ka, Pannon Large and Pannon White rabbits with respect to haplotypes found in other wild and domestic rabbit populations (see the legend for a detailed description). Diagram was constructed based on mtDNA haplotypes identified by polymorphism analysis of a 332-bp fragment of mtDNA (RRS: NC001913 positions 15492–15824). Circles are proportional to haplotype frequency, the black points represent hypothetical sequences that were not observed, while the number of mutations separating nodes are given near branches in parentheses. Names of the presented haplotypes contain identification, accession number and origin (abbreviation) with the exception of Pannon breeds that are given by full name.

heterogeneity of maternal origin is in accordance with the formation history of the breed, as PW is a synthetic breed derived from 2 breeds, the Californian and New Zealand rabbits. H1 is by far the most represented haplotype in rabbits, and a number of very diverse rabbit populations share this haplotype (Asian domestic, Australian wild, European domestic and European wild). H2 is the second most frequent haplotype, with sequences found in Australian wild, European domestic and European wild populations. More detailed description of the haplotype origin is presented in Supplement Table S1.

Cytoplasmic and mtDNA haplotype effects

Carcass trait

The estimated contribution of cytoplasmic maternal variance to the phenotypic variance (cyt^2) and the contribution of D-loop mtDNA haplotype variance to the phenotypic variance ($Hcyt^2$) were zero (models 9 and 10), indicating that neither maternal lineage nor D-loop mtDNA haplotype effects were present in PW (Table 4). There was no significant

Table 5: Estimated variance components (V) and genetic parameters for additive genetic (A), cytoplasmic (maternal and paternal) and environmental effects (E) for litter size traits in Pannon rabbit breeds.

Breed	Traits	Model	V_A	h^2	V_{mcyt}	$mcyt^2$	V_{pcyt}	$pcyt^2$	V_{pe}	p^2	V_E	e^2	MSE
Pannon White		1	0.674	0.076	-	-	-		0.713	0.080	7.529	0.844	6.812
		2	0.674	0.076	0.000	0.000	-		0.712	0.080	7.529	0.844	6.812
	NBA	3	0.672	0.075	-	-	0.012	0.001	0.710	0.080	7.523	0.844	6.802
		4	0.672	0.075	0.000	0.000	0.012	0.001	0.711	0.080	7.523	0.844	6.802
		1	0.024	0.020	-	-	-		0.024	0.020	1.135	0.960	1.086
		2	0.024	0.020	0.000	0.000	-		0.024	0.020	1.135	0.960	1.086
	NBD	3	0.024	0.020	-	-	0.000	0.000	0.024	0.020	1.135	0.960	1.086
		4	0.024	0.020	0.000	0.000	0.000	0.000	0.024	0.020	1.135	0.960	1.086
		1	0.695	0.076	-	-	-		0.760	0.083	7.652	0.840	6.910
		2	0.695	0.076	0.000	0.000	-		0.760	0.084	7.652	0.840	6.910
	TNB	3	0.694	0.076	-	-	0.005	0.001	0.759	0.083	7.649	0.840	6.906
		4	0.694	0.076	0.000	0.000	0.005	0.001	0.759	0.083	7.649	0.840	6.906
Pannon Ka		1	0.754	0.087	-	-	-		0.647	0.075	7.270	0.838	6.545
		2	0.755	0.087	0.000	0.000	-		0.647	0.075	7.270	0.838	6.544
	NBA	3	0.760	0.087	-	-	0.000	0.000	0.647	0.075	7.270	0.838	6.544
		4	0.760	0.087	0.000	0.000	0.027	0.003	0.644	0.074	7.266	0.835	6.539
		1	0.060	0.047	-	-	-		0.000	0.000	1.217	0.953	1.163
		2	0.060	0.047	0.000	0.000	-		0.000	0.000	1.217	0.953	1.163
	NBD	3	0.060	0.047	-	-	0.000		0.000	0.000	1.217	0.953	1.163
		4	0.060	0.047	0.000	0.000	0.000		0.000	0.000	1.217	0.953	1.163
		1	0.885	0.100	-	-	-		0.638	0.072	7.288	0.827	6.542
		2	0.887	0.101	0.000	0.000	-		0.637	0.072	7.289	0.827	6.542
	TNB	3	0.887	0.101	-	-	0.000		0.638	0.072	7.289	0.827	6.542
		4	0.887	0.101	0.000	0.000	0.000		0.638	0.072	7.288	0.827	6.542
Pannon Large		1	0.852	0.088	-	-	-		1.220	0.126	7.630	0.786	6.694
		2	0.853	0.088	0.000	0.000	-		1.219	0.126	7.630	0.786	6.694
	NBA	3	0.853	0.088	-	-	0.000		1.219	0.126	7.630	0.786	6.694
		4	0.853	0.088	0.000	0.000	0.000		1.219	0.126	7.630	0.786	6.694
		1	0.088	0.032	-	-	-		0.036	0.013	2.624	0.955	2.492
		2	0.088	0.032	0.000	0.000	-		0.036	0.013	2.624	0.955	2.492
	NBD	3	0.087	0.032	-	-	0.004	0.001	0.034	0.012	2.624	0.954	2.491
		4	0.087	0.032	0.000	0.000	0.004	0.001	0.037	0.012	2.624	0.954	2.491
		1	0.877	0.083	-	-	-		1.250	0.118	8.466	0.799	7.466
		2	0.880	0.083	0.000	0.000	-		1.250	0.118	8.464	0.799	7.466
	TNB	3	0.878	0.083	-	-	0.000		1.250	0.118	8.465	0.799	7.465
		4	0.878	0.083	0.000	0.000	0.000		1.250	0.118	8.465	0.799	7.465

NBA is number of kits born alive, NBD is number of kits born dead and TNB is total number of kits born; V_A, V_{mcyt}, V_{pcyt}, V_{Pe} and V_E are additive, cytoplasmic maternal, cytoplasmic paternal, permanent environmental, and residual variances, respectively; h^2 is the narrow sense heritability; $mcyt^2$ is the contribution of cytoplasmic maternal variance to the phenotypic variance; $pcyt^2$ is the contribution of cytoplasmic paternal variance to the phenotypic variance; p^2 is the contribution of permanent environmental variance to the phenotypic variance; e^2 is the contribution of residual variance to phenotypic variance; MSE is mean squared error.

effect of haplotype when haplotypes were compared as fixed effect. The estimated heritabilities (h^2) of TMV, the trait introduced as a selection criterion in 2004, were moderate, ranging from 0.275±0.02 to 0.302±0.02. Ratios of the random litter effects to the phenotypic variance were small for TMV, ranging from 0.059±0.01 to 0.076±0.01. The smallest MSE values, representing goodness of fit, were obtained in models with cytoplasmic effects. However, this latter result has no importance, as the effects of these components were equal to zero.

Table 6: Estimated variance components (V) for additive genetic (A), D-loop mtDNA (maternal and paternal) and environmental effects (E) for litter size traits in Pannon White rabbit.

Traits	Model	V_A	h^2	V_{Hma}	Hma^2	V_{Hpa}	Hpa^2	V_{pe}	p^2	V_E	e^2	MSE
NBA	5	0.606	0.071	0.000	0.000	-	-	0.736	0.086	7.252	0.844	6.463
	6	0.617	0.071	-	-	0.006	0.001	0.716	0.083	7.310	0.845	6.402
	7	0.652	0.074	0.009	0.001	0.000	0.000	0.739	0.084	7.415	0.841	6.459
NBD	5	0.038	0.031	0.000	0.000	-	-	0.008	0.006	1.193	0.963	1.131
	6	0.029	0.023	-	-	0.000	0.000	0.020	0.016	1.211	0.962	1.140
	7	0.035	0.027	0.000	0.000	0.000	0.000	0.015	0.012	1.251	0.961	1.168
TNB	5	0.602	0.068	0.000	0.00000	-	-	0.817	0.093	7.377	0.839	6.559
	6	0.628	0.070	-	-	0.002	0.000	0.818	0.092	7.474	0.838	6.518
	7	0.637	0.070	0.005	0.001	0.000	0.000	0.833	0.092	7.601	0.838	6.611

NBA is number of kits born alive, NBD is number of kits born dead and TNB is total number of kits born; V_A, V_{Hma}, V_{Hpa}, V_{Pe} and V_E are additive, D-loop mtDNA maternal haplotype, D-loop mtDNA paternal haplotype, permanent environmental, and residual variances, respectively; h^2 is narrow sense heritability; Hma^2 is the contribution of D-loop mtDNA maternal haplotype variance to the phenotypic variance; Hpa^2 is the contribution of D-loop mtDNA paternal haplotype variance to the phenotypic variance; p^2 is the contribution of permanent environmental variance to the phenotypic variance; e^2 is the contribution of residual variance to phenotypic variance; MSE is mean squared error.

Litter size traits

Estimated additive genetic variances, cytoplasmic or D-loop mtDNA (analysed from maternal and paternal side), permanent environmental and residual variances by the magnitude and ratios (compared to the phenotypic variance) are summarised in Tables 5 and 6 for litter traits. The best model fits (smallest MSE values) were obtained in models with cytoplasmic effects. Note that in Model 5, 6 and 7 in PW rabbits sample sizes were reduced. However, both estimated cytoplasmic effects (maternal - $mcyt^2$ and paternal - $pcyt^2$) ranged from zero (0.0%) to negligible (0.3%±0.003), obtained for p^2 for NBA in Pannon Ka (see Table 5. for the details). Similar results, with negligible contribution to phenotypic variance, from 0.1%±0.001 (maternal - Hma^2) to 0.02-0.1%±0.003-0.001 (paternal - Hpa2), were obtained for D-loop mtDNA haplotypes. The estimated heritabilities of Pannon rabbits for NBA ranged from 0.071±0.0078-0.088±0.0167, 0.020-0.047±0.0037-0.0078 (NBD) and 0.068-0.101±0.0075-0.0161 (TNB). A similar trend was observed for variance components of permanent environmental effect, ranging for NBA in 0.075-0.126±0.0062-0.0149, for NBD in 0.000-0.020±0.0000-0.0094 and for TNB in 0.072-0.118±0.0066-0.0145.

DISCUSSIONS AND CONCLUSION

Although encoding for a small number of genes, the effects of mitogenome variation on production traits are reported in a number of animal domestic species. Until now, the impact of mitogenome on production traits had never been analysed in rabbits. In this study, we analysed the effects of mitogenome variation on litter size traits (NBA, NBD and TNB) and on one carcass trait (TMV) measured *in vivo* by computer tomography (CT). We began our analysis by testing cytoplasmic effects on production traits, where the impact of maternal lineages was analysed for both does and mating bucks. For all traits and breeds the impact of cytoplasmic inheritance was absent or negligible. Moreover, in all 3 Pannon breeds we determined D-loop mtDNA haplotypes for each maternal lineage. Overall, there were only 2 different haplotypes present in PW (H1 and H2), while in the other 2 breeds (PK and PL) only H1 was present - if we exclude a small number of rabbits in PK breed with non-consistent mtDNA segregation in a pedigree. We also found no significant contribution of D-loop mtDNA sequence polymorphism on any of production traits analysed in PW. The lack of information on complete mitogenome polymorphism is the most likely explanation for the observed results. Our molecular analysis was restricted to only 332 bps and it is possible that complete mitogenome sequence variation is higher than that observed for D-loop mtDNA sequence (332 bps). On a 332 bp long sequence, haplotypes H1 and H2 do belong to the most common haplotypes in rabbits.

However, we are not able to say that segregating mitogenome variation is optimal with respect to production traits, or that they are free of detrimental mutations. Thus, the magnitude of the potential benefits of the introduction or alteration of mitogenome variation using gene editing techniques (Hickey *et al.,* 2016), in rabbit breeding programmes remains an open question for future research.

Acknowledgments: This study was supported by the EFOP-3.6.1-16-2016-00007 project, the CEEPUS scholarship for the year 2016 and the Croatian Science Foundation under Project IP-11-2013_9070 ("Utilisation of the whole mitogenome in cattle breeding and conservation genetics", http://mitotauromics.agr.hr/). This research was partly supported by the European Regional Development Fund under the grant KK.01.1.1.01.0009 (DATACROSS).

REFERENCES

Al-Saef A.M., Khalil M.H., Al-Homidan A.H., Al-Dobaib S.N., Al-Sobayil K.A., García M.L., Baselga M. 2008. Crossbreeding effects for litter and lactation traits in a Saudi project to develop new lines of rabbits suitable for hot climates. *Livest. Sci., 118: 238-246. https://doi.org/10.1016/j.livsci.2008.01.025*

Bandelt H., Forster P., Röhl A. 1999. Median-joining networks for inferring intraspecific phylogenies. *Mol. Biol. Evol., 16: 37-48. https://doi.org/10.1093/oxfordjournals.molbev.a026036*

Bell B.R., Mcdaniel B.T., Robison O.W. 1985. Effects of cytoplasmic inheritance on production traits of dairy-cattle. *J. Dairy Sci., 68: 2038-2051. https://doi.org/10.3168/jds.S0022-0302(85)81066-3*

Boettcher P.J., Freeman A.E., Johnston S.D., Smith R.K., Beitz D.C. McDaniel B.T. 1996a. Relationships between polymorphism for mitochondrial deoxyribonucleic acid and yield traits of Holstein cows. *J. Dairy Sci. 79: 647-654. https://doi.org/10.3168/jds.S0022-0302(96)76410-X*

Boettcher P. J., Steverink D.W.B., Beitz D.C., Freeman A.E., McDaniel B.T. 1996b. Multiple herd evaluation of the effects of maternal lineage on yield traits of Holstein Cattle. *J. Dairy Sci., 79: 655-662. https://doi.org/10.3168/jds.S0022-0302(96)76411-1*

Boettcher P. J., Kuhn M.T., Freeman A.E. 1996c. Impacts of cytoplasmic inheritance on genetic evaluations. *J. Dairy Sci., 79: 663-675. https://doi.org/10.3168/jds.S0022-0302(96)76412-3*

Boettcher P. J., Gibson J. P. 1997. Estimation of variance of maternal lineage effects among Canadian Holsteins. *J. Dairy Sci., 80: 2167-2176. https://doi.org/10.3168/jds.S0022-0302(97)76164-2*

Čačić M., Cubric-Curik V., Ristov S., Curik, I. 2014. Computational approach to utilisation of mitochondrial DNA in the verification of complex pedigree errors. *Livest. Sci., 169: 42-47. https://doi.org/10.1016/j.livsci.2014.09.009*

Chen X., Wang D., Xiang H., Dun W., Brahi D. O. H., Yin T., Zhao X. 2017. Mitochondrial DNA T7719G in tRNA-Lys gene affects litter size in Small-tailed Han sheep. *J. Anim. Sci. Biotechnol., 8: 31. https://doi.org/10.1186/s40104-017-0160-x*

Fernández A.I., Alves E., Fernández A., de Pedro E., López-García M.A., Ovilo C., Rodríguez M.C., Silió L. 2008. Mitochondrial genome polymorphisms associated with longissimus muscle composition in Iberian pigs. *J Anim Sci., 86: 1283-1290. https://doi.org/10.2527/jas.2007-0568*

Gibson J.P., Freeman A.E., Boettcher P.J. 1997. Cytoplasmic and mitochon-drial inheritance of economic traits in cattle. Livest. *Prod. Sci., 47: 115-124. https://doi.org/10.1016/S0301-6226(96)00023-1*

Groeneveld E. 1990. PEST Users' Manual. *Institute of Animal Husbandry and Animal Behaviour Federal Research Centre, Neustadt, Germany. 1-80.*

Groeneveld E., Kovac M., Mielenz N. 2008. VCE User's Guide and Reference Manual. *Version 6.0. Institute of Farm Animal Genetics, Neustadt, Germany. 1-125*

Gutiérrez J.P., Goyache F., Cervantes I. 2010. ENDOG v4.8. A computer program for monitoring genetic variability of populations using pedigree information. User's Guide. *Departamento de Producción Animal. Facultad de Veterinaria. Universidad Complutense de Madrid. Área de Genetica y Reproducción Animal SERIDASomió. 1-45.*

Gyovai, P., I. Nagy, Zs. Gerencsér, Zs. Matics, I. Radnai, T. Donkó, Á. Bokor, J. Farkas, Szendrő Zs. 2011. Genetic parameters for litter weight, average daily gain and thigh muscle volume measured by in vivo Computer Tomography technique in Pannon White rabbits. *Livest. Sci., 144: 119-123. https://doi.org/10.1016/j.livsci.2011.11.006*

Hanford K.J., Snowder G.D., Van Vleck L.D. 2003. Models with nuclear, cytoplasmic, and environmental effects for production traits of Columbia sheep. *J. Anim. Sci., 81: 1926-1932. https://doi.org/10.2527/2003.8181926x*

Hickey J.M., Bruce, C., Whitelaw, A., Gorjanc G. 2016. Promotion of alleles by genome editing in livestock breeding programmes. *J. Anim. Breed. Genet., 133: 83-84. https://doi.org/10.1111/jbg.12206*

Hill W.G., Mulder H.A. 2010. Genetic analysis of environmental variation. *Genet. Res. (Camb.), 92: 381-395. https://doi.org/10.1017/S0016672310000546*

John J.C., Jokhi R.P., Barratt C.L. 2005. The impact of mitochondrial genetics on male infertility. *Int. J. Androl., 28: 65-73. https://doi.org/10.1111/j.1365-2605.2005.00515.x*

Kennedy B.W. 1986. A further look at evidence for cytoplasmic inheritance for production traits in dairy cattle. *J. Dairy. Sci., 69: 3100-3105. https://doi.org/10.3168/jds.S0022-0302(86)80773-1*

Kumar S., Stecher G., Tamura K. 2016. MEGA7: Molecular Evolutionary Genetics Analysis version 7.0. *Mol. Biol. Evol., 33: 1870-1874. https://doi.org/10.1093/molbev/msw054*

Leigh, J. W. and Bryant, D. 2015. popart: full-feature software for haplotype network construction. *Methods Ecol. Evo., 6: 1110-1116. https://doi.org/10.1111/2041-210X.12410*

Li S., Aggrey S.E., Zadworny D., Fairfull W., Kuhnlein U. 1998. Evidence for a genetic variation in the mitochondrial genome affecting traits in White Leghorn chickens. *J. Heredity, 89: 222-226. https://doi.org/10.1093/jhered/89.3.222*

Librado P., Rozas J. 2009. DnaSP v5: A software for comprehensive analysis of DNA polymorphism data. *Bioinformatics, 25: 1451-1452. https://doi.org/10.1093/bioinformatics/btp187*

Liu C., Yang Q., Hwang S.J., Sun F., Johnson A. D., Shirihai, O., Ramachandran S., Vasan D.L, Schwartz F. 2012. Association of Genetic Variation in the Mitochondrial Genome with Blood Pressure and Metabolic Traits. *Hypertension, 60: 949-956. https://doi.org/10.1161/HYPERTENSIONAHA.112.196519*

Matics Zs., Nagy I., Gerencsér Zs., Radnai I., Gyovai P., Donkó T., Dalle Zotte A., Curik I., Szendrő Zs. 2014. Pannon breeding program at Kaposvár University. *World Rabbit Sci. 22: 287-300. https://doi.org/10.4995/wrs.2014.1511*

Melo-Ferreira J., Alves P.C., Freitas H., Ferrand N., Boursot P. 2009. The genomic legacy from the extinct *Lepus timidus* to the three hare species of Iberia: contrast between mtDNA, sex chromosomes and autosomes. *Mol. Ecol., 18: 2643-2658. https://doi.org/10.1111/j.1365-294X.2009.04221.x*

Mezzadra C.A, Melucci L.M, Corva P.M., Valiente S.L., Rípoli M.V., Lirón P., Giovambattista G. 2005. Effects of cytoplasmic inheritance on preweaning traits of Hereford cattle. *Genet. Mol. Biol., 28: 357-362. https://doi.org/10.1590/S1415-47572005000300003*

Nagy I., Radnai I., Nagyné-Kiszlinger H., Farkas J., Szendrő Zs. 2011. Genetic parameters and genetic trends of reproduction traits in synthetic Pannon rabbits using repeatability and multi-trait animal models. *Archiv Tierzucht, 54: 297-307. https://doi.org/10.5194/aab-54-297-2011*

Nagy I., Gyovai P., Radnai I., Kiszlinger H., Farkas J., Szendrő Zs. 2013a. Genetic parameters, genetic trends and inbreeding depression of growth and carcass traits in Pannon terminal line rabbits. *Archiv Tierzucht, 56: 191-199. https://doi.org/10.7482/0003-9438-56-018*

Nagy I., Gorjanc G., Curik I., Farkas J., Kiszlinger H., Szendrő Zs. 2013b. The contribution of dominance and inbreeding depression in estimating variance components for litter size in Pannon White rabbits. *J. Anim. Breed. Genet., 130: 303-311. https://doi.org/10.1111/jbg.12022*

Nagy, I., Farkas, J., Curik, I., Gorjanc, G., Gyovai, P., Szendrő, Zs., 2014 - Estimation of additive and dominance variance for litter size components in rabbits. *Czech J. Anim. Sci., 59: 182-189. https://doi.org/10.17221/7342-CJAS*

Pierpaoli M., Riga F., Trocchi V., Randi E. 1999. Species distinction and evolutionary relationships of the Italian hare (*Lepus corsicanus*) as described by mitochondrial DNA sequencing. *Mol. Ecol., 8: 1805-1817. https://doi.org/10.1046/j.1365-294x.1999.00766.x*

Pun A., Goyache F., Cervantes I., Gutiérrez J.P. 2012. Cytoplasmic line effects for birth weight and preweaning growth traits in the Asturiana de los Valles beef cattle breed. *Livest. Sci., 143: 177-183. https://doi.org/10.1016/j.livsci.2011.09.008*

Ristov S., Brajkovic V., Cubric-Curik V., Michieli I., Curik I. 2016. MaGelLAn 1.0: a software to facilitate quantitative and population genetic analysis of maternal inheritance by combination of molecular and pedigree information. *Genet Sel Evol., 48: 65. https://doi.org/10.1186/s12711-016-0242-9*

Ruiz-Pesini E., Lapeña A.C., Díez-Sánchez C., Pérez-Martos A., Montoya J., Alvarez E., Díaz M., Urriés A., Montoro L., López-Pérez M.J., Enríquez J.A. 2000. Human mtDNA haplogroups associated with high or reduced spermatozoa motility. *Am. J. Hum. Genet., 67: 682-696. https://doi.org/10.1086/303040*

Snowder G. D., Hanford K. J., Van Vleck L. D. 2004. Comparison of models including cytoplasmic effects for traits of Rambouillet sheep. *Faculty Papers and Pub. Anim. Sci., 90:159-166. https://doi.org/10.1016/j.livprodsci.2004.03.003*

Szwaczkowski T., Bednarczyk M., Kielczewski K. 1999. Direct, maternal and cytoplasmic variance estimates of egg production traits in laying hens. *J. Anim. Feed. Sci., 8: 589-598. https://doi.org/10.22358/jafs/69183/1999*

Tsai T.S., Rajasekar S., John J.C.T. 2016. The relationship between mitochondrial DNA haplotype and the reproductive capacity of domestic pigs (*Sus scrofa domesticus*). *BMC Genetics, 17: 67. https://doi.org/10.1186/s12863-016-0375-4*

Van Vleck L.D. 2000. Selection index and introduction to mixed models methods. *CRC Press In., Boca Raton, Florida 33431. 19: 225-231.*

Yen N.T., Lin C.S., Ju C.C., Wang S.C., Huang M.C. 2007. Mitochondrial DNA polymorphism and determination of effects on reproductive trait in pigs. *Reprod. Domest. Anim. 42: 387-92. https://doi.org/10.1111/j.1439-0531.2006.00797.x*

Yu G., Xiang H., Tian J., Yin J., Pinkert C.A., Li Q., Zhao X. 2015. Mitochondrial Haplotypes Influence Metabolic Traits in Porcine Transmitochondrial Cybrids. *Sci. Rep., 19: 13118-10. https://doi.org/10.1038/srep13118*

Wallace D. C. 1999. Mitochondrial diseases in man and mouse. *Science, 283: 1482-1488. https://doi.org/10.1126/science.283.5407.1482*

Zhao X., Wu N., Zhu Q., Gaur U., Gu T., Li D. 2015. High-altitude adaptation of Tibetan chicken from MT-COI and ATP-6 perspective. *Mitochondrial DNA, Early Online: 1-9. https://doi.org/10.3109/19401736.2015.1015006*

Supplement Table S1: Description of rabbit (*Oryctolagus cuniculus*) haplotype sequences presented in Figure 1.

Accession #	Origin	Haplotype	Reference	Description
AJ293831	France	H6	Bolet *et al.,* 2000.	Domestic Fauve de Bourgogne
AJ293832	Belgium	H7	Bolet *et al.,* 2000.	Domestic Belgian hare
AJ293833	France	H8	Bolet *et al.,* 2000.	Domestic Fauve de Bourgogne
AJ293834	France	H9	Bolet *et al.,* 2000.	Domestic Argente de Champagne
AJ293835	Great Britain	H10	Bolet *et al.,* 2000.	Domestic English
AJ293836	Belgium	H11	Bolet *et al.,* 2000.	Domestic Flemish giant
AJ293837	France	H12	Bolet *et al.,* 2000.	Domestic Fauve de Bourgogne
AJ293838	Hungary	H13	Bolet *et al.,* 2000.	Domestic Hungarian Giant
AJ293839	France	H14	Bolet *et al.,* 2000.	Domestic French Lop
AJ293840	France	H15	Bolet *et al.,* 2000.	Domestic French Lop
AJ293841	France	H16	Bolet *et al.,* 2000.	Domestic French Lop
AJ293843	Austria	H17	Bolet *et al.,* 2000.	Domestic Vienna White
AJ293844	Belgium	H18	Bolet *et al.,* 2000.	Domestic Flemish Giant
U62924	Australia	H4	Fuller *et al.,* 1997..	Wild rabbit
U62925	Australia	H1	Fuller *et al.,* 1997	Wild rabbit
U62926	Australia	H16	Fuller *et al.,* 1997	Wild rabbit
U62927	Australia	H2	Fuller *et al.,* 1997	Wild rabbit
NC_001913	Unknown	H1	Gissi *et al.,* 1998.	Rabbit reference sequence
AF534080	China	H1	Long, *et al.,* 2003.	Qixing
AF534081	China	H1	Long, *et al.,* 2003	Haerbin White
AF534082	China	H1	Long, *et al.,* 2003	Zhenhai thick-hair Angora
AF534083	China	H1	Long, *et al.,* 2003	Big ear brown rabbit
AF534085	Belgium	H1	Long, *et al.,* 2003	Belgium
AF534092	China	H1	Long, *et al.,* 2003	Sichuan White
AF534094	Germany	H1	Long, *et al.,* 2003	Rex
AF534095	Germany	H1	Long, *et al.,* 2003	Angora
AF534096	Germany	H1	Long, *et al.,* 2003	Zika
AF534097	China	H1	Long, *et al.,* 2003	Fujian Brown
AF534098	China	H1	Long, *et al.,* 2003	Taihang Moutain
AF534099	China	H3	Long, *et al.,* 2003	Yufeng Brown
AF534100	Germany	H2	Long, *et al.,* 2003	Zika (Germany great line)
AF534101	Germany	H2	Long, *et al.,* 2003	Rex
AF534103	China	H4	Long, *et al.,* 2003	Zhenhai thick-hair Angora
AF534104	Japan	H1	Long, *et al.,* 2003	Japanese White
AF534105	China	H1	Long, *et al.,* 2003	Yufeng Brown
AF534107	Germany	H5	Long, *et al.,* 2003	Zika
KY977609	Hungary	H1	This study	Pannon Large
KY977634	Hungary	H1	This study	Pannon Ka
KY977665	Hungary	H1	This study	Pannon White
KY977670	Hungary	H2	This study	Pannon White
Z83340	Spain/Portugal	H19	van der Loo *et al.,* 1997.	Wild rabbit
Z83341	Spain/Portugal	H20	van der Loo *et al.,* 1997.	Wild rabbit
Z83342	Spain/Portugal	H21	van der Loo *et al.,* 1997.	Wild rabbit

Supplement Table S1 continues on next page

Supplement Table S1 continues from previous page

Accession #	Origin	Haplotype	Reference	Description
Z83343	Spain/Portugal	H22	van der Loo *et al.,* 1997.	Wild rabbit
Z83344	Spain/Portugal	H23	van der Loo *et al.,* 1997.	Wild rabbit
Z83346	Spain	H24	van der Loo *et al.,* 1997.	Wild rabbit
Z83347	Spain	H25	van der Loo *et al.,* 1997.	Wild rabbit
Z83348	Spain	H26	van der Loo *et al.,* 1997.	Wild rabbit
Z83350	Spain	H27	van der Loo *et al.,* 1997.	Wild rabbit
Z83352	Spain	H16	van der Loo *et al.,* 1997.	Wild rabbit
Z83354	Spain	H28	van der Loo *et al.,* 1997.	Wild rabbit
Z83355	Spain	H29	van der Loo *et al.,* 1997.	Wild rabbit
Z83356	Spain	H30	van der Loo *et al.,* 1997.	Wild rabbit
Z83357	Spain	H31	van der Loo *et al.,* 1997.	Wild rabbit
Z83358	Spain	H32	van der Loo *et al.,* 1997.	Wild rabbit
Z83359	Spain	H33	van der Loo *et al.,* 1997.	Wild rabbit
Z83360	Spain	H34	van der Loo *et al.,* 1997.	Wild rabbit
Z83361	Spain	H35	van der Loo *et al.,* 1997.	Wild rabbit
Z83362	Spain	H36	van der Loo *et al.,* 1997.	Wild rabbit
Z83363	Spain	H37	van der Loo *et al.,* 1997.	Wild rabbit
Z83364	Spain	H38	van der Loo *et al.,* 1997.	Wild rabbit
Z83365	Spain	H2	van der Loo *et al.,* 1997.	Wild rabbit
Z83366	Spain	H4	van der Loo *et al.,* 1997.	Wild rabbit
Z83367	Spain	H1	van der Loo *et al.,* 1997.	Wild rabbit

Bolet G., Brun J.M., Monnerot M., Abeni F., Arnal C., Arnold J., Bell D., Bergoglio G., Besenfelder U., Bosze S., Boucher S., Chanteloup N., Ducourouble M.C., Durand-Tardif M.H., Esteves P.J., Ferrand N., Gautier A., Haas C., Hewitt G., Jehl N., Saleil G. 2000. Evaluation and conservation of European rabbit (*Oryctolagus cuniculus*) genetic resources. First results and inferences. *World Rabbit Science, 8 (sp): 281-315.*

Fuller S.J., Wilson J.C., Mather P.B. 1997. Patterns of differentiation among wild rabbit populations *Oryctolagus cuniculus* L. arid and semiarid ecosystems of north-eastern Australia. *Molecular Ecology, 2: 145-153. https://doi.org/10.1046/j.1365-294X.1997.00167.x*

Gissi C., Gullberg A., Arnason U. 1998. The complete mitochondrial DNA sequence of the rabbit, *Oryctolagus cuniculus. Genomics, 2: 161-169. https://doi.org/10.1006/geno.1998.5282*

Long J.R., Qiu X.P., Zeng F.T., Tang L.M., Zhang Y.P. 2003. Origin of rabbit (*Oryctolagus cuniculus*) in China: evidence from mitochondrial DNA control region sequence analysis. *Animal Genetics, 34: 82-87. https://doi.org/10.1046/j.1365-2052.2003.00945.x*

van der Loo W., Mougel F., Sánchez M.S., Bouton C., Castien E., Soriguer R., Hamers R., Monnerot M. 1997. Evolutionnary patterns at the antibody constant region in rabbit (*Oryctolagus cuniculus*): characterisation of endemic b-locus allotypes and their frequency correlation with major mitochondrial gene types in Spain. *Gibier Faune Sauvage, 14: 427-449.*