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DOMESTIC RABBIT *Oryctolagus cuniculus* var. *domestica* L. AS A MODEL IN THE STUDY OF DOMESTICATION AND BIOMEDICAL RESEARCHES

(review)

E.S. SHCHUKINA¹, G.Yu. KOSOVSKY¹, V.I. GLAZKO^{1, 2}, I.S. KASHAPOVA¹, T.T. GLAZKO^{1, 2}

¹Afanas'ev Research Institute of Fur-Bearing Animal Breeding and Rabbit Breeding, 6, ul. Trudovaya, pos. Rodniki, Ramenskii Region, Moscow Province, 140143 Russia, e-mail elena.rainis.lis@yandex.ru, gkosovsky@mail.ru, i-kashapova@rambler.ru

²Timiryazev Russian State Agrarian University—Moscow Agrarian Academy, 49, ul. Timiryazevskaya, Moscow, 127550 Russia, e-mail vigvalery@gmail.com (✉ corresponding author), tglazko@rambler.russia, e-mail ktqrip7@yandex.ru
ORCID:

Shchukina E.S. orcid.org/0000-0002-2465-7184

Kashapova I.S. orcid.org/0000-0002-6360-0025

Kosovskii G.Yu. orcid.org/0000-0003-3808-3086

Glazko T.T. orcid.org/0000-0002-3879-6935

Glazko V.I. orcid.org/0000-0002-8566-8717

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Abstract

The domestic rabbit (*Oryctolagus cuniculus* var. *domestica* L.) belongs to the few domesticated species in which the wild ancestral species exists simultaneously with the domesticated one (M. Carneiro, 2014) that allows us to study the mechanisms underlying the processes of domestication. It should be noted that the genetic basis of domestication syndrome is still insufficiently studied (M.A. Zeder, 2006-2017). It is assumed that domestication is a unique form of symbiosis between humans and domesticated species that form a common habitat niche (M.A. Zeder, 2012). Research of symbiotic partners of such a niche allows us to accumulate information about the mechanisms of adaptation to it, including humans. In this regard, it is difficult to overestimate the importance of studying the domestic rabbit, because it has remained one of the main models in biomedical research for many decades (K.M. El-Bayomi, 2013). The unique physiological features of the rabbit explain its widespread use in the study of many human diseases. At the same time, we have not found any works that systematize current information on the fundamental biology of this domesticated species in comparison with its wild ancestral form. The purpose of this review is to summarize data on the population genetic structure (M. Carneiro, 2014; A.D. Stock, 1976), distribution of genomic elements (M. Carneiro, 2011), composition of microbiomes (M.S. Gómez-Conde, 2009), morphometric characteristics and physiological features (S.N. Bogolyubskii, 1959) of the domestic rabbit and ancestral subspecies of the European rabbit, including those that determine the value of *O. cuniculus* var. *domestica* not only as an economically valuable species, but also as a model object in various fields of biomedicine. The presented comparative analysis allows us to identify a number of phenotypic characteristics (J.L. Hendrikse, 2007; I. Brusini, 2018; P.S. Ungar, 2010), as well as a group of molecular genetic markers of genomic DNA, differentiating the domestic rabbit from the ancestral species (M. Sparwel, 2019). Distribution of alleles of different mobile genetic elements, microsatellites, separate structural genes involved in the domestication process of domestic rabbit, can improve the efficiency of genetic resources management of not only this species but also other objects that are used in biomedical research, and for solving problems of selection work.

Keywords: domestication syndrome, wild rabbits, domestic rabbits, DNA markers, endogenous retroviruses, polylocus genotyping, microbiota

The study of the genetic structure of domesticated species is a prerequisite for the development of methods for managing the genetic resources of economically valuable animals. Domestic rabbit *Oryctolagus cuniculus* var. *domestica* L. belongs to those rare domesticated species in which the wild ancestral species exists simultaneously with the domesticated one, which allows studying the mechanisms

underlying domestication.

Rabbit breeding is currently actively developing, and, according to IndexBox, Inc. (Great Britain), the growth of world production of rabbit meat will maintain the current trend with the expected annual growth of the market about +2.3% (up to 1.8 million tons by 2025) (<https://meatinfo.ru>). At the same time, we did not find any works summarizing modern information on the fundamental biology of this domesticated species.

This review aimed to compare the population genetic structure, distribution of genomic elements and phenotypic features of the domestic rabbit and its ancestral subspecies, the European rabbit, and also to summarize data on microbiome composition and physiological characteristics due to which the domestic rabbit is a model in various fields of biomedicine

Domestic rabbit as an object of research and use. The domestic rabbit (*Oryctolagus cuniculus* var. *domestica* L.) has shared a common niche with humans for a long time. Domestication is a quantitative trait which varies from animals experiencing anthropogenic pressure to the most domesticated and forming a common niche with humans [1]. Today, there is no consensus on what domestication and domestication syndrome are, though this syndrome is common for taxonomically distant species [2-4]. According to a number of researchers [2], domestication is a unique symbiosis between humans and domesticated species that coexist in a single ecological niche.

The new geological period in which human activity turned into a planetary transforming force, called the Anthropocene [5], affects the adaptation of animals to habitat conditions via interfering with their life cycles. In general, the domestication model indicates that the target of selection is not one species, but their community, that is, there is a coevolution of animals, humans, and other symbionts, including those that are part of the microbiome in different species [1]. The study of the mechanisms of domestication makes a significant contribution to understanding appearance of new forms, artificial selection, methodology for managing gene pools, breed formation and other microevolutionary processes.

The European rabbit (*Oryctolagus cuniculus* L.) is the only recognized ancestor of the domestic rabbit, which, in its turn, is an important agricultural species with high-value dietary meat 90% of which can be utilized by the human, high productivity, early maturity, relatively simple use in fur farming, and also a unique biomedical model due to the peculiarities of physiology [6]. Rabbits as laboratory mammals are much closer genetically and physiologically to humans. In addition, high fertility and a short reproductive period make them the most convenient model for research as compared to other domesticated mammalian species.

Due to the short life expectancy, relatively short gestation periods, multiple births, low cost and availability of genomic and proteomic information, the domestic rabbit fills the gap between small laboratory animals, the mice and rats, and larger animals, the dogs and monkeys, in extrapolation of model experimental data to human. In some cases, this plays a crucial role, for example, in preclinical testing of drugs and diagnostic methods [7]. One of the visual contributions of rabbits to medicine is the discovery of statin, the most powerful lipid-lowering drug [8]. With the development of therapeutic methods, it became obvious that many human diseases cannot be properly investigated in small mouse-like rodents. Many clinical trials have been unsuccessful, perhaps due to use of these models in the experiments. Rabbits are models for studying human diseases and elucidating those specific issues that cannot be solved in rodents, which makes rabbit valuable in both biomedical and fundamental research [9]. An example is hereditary diseases that are widespread in humans (aortic atherosclerosis, cataracts, hypertension, hypertrophic cardiomyopathy, epilepsy, osteoporosis, etc.). The production

of transgenic rabbits and those with knockout genes is a new impetus for the development of both therapeutic and diagnostic strategies in the future [10].

It can be expected that a comparative analysis of the genome of the rabbit and other mammals will further increase its usefulness as a biological model. The study of epigenetic changes in regulatory genomic elements will contribute to the detection of gene networks underlying the adaptation of animals to environmental stress factors, and sequencing of rabbit genomes will make it possible to identify and compare critical regulatory elements of this process, structural genes and their interactions in rodents, lagomorphs and primates.

The domestic rabbit is one of the youngest domestic species. It is characterized by an exceptionally high phenotypic diversity. More than 200 breeds of rabbits are known [11], which are bred for both commercial and research purposes [12-15]. Commercial interests include the production of meat, fur, wool, and therapeutic proteins; in addition, rabbits are used as pets and companions [16-18]. At present, breeding continues, including a significant contribution of marker assistance selection (MAS) and genomic selection based on identification of SNP polymorphisms of structural genes and regulatory genomic elements controlling various metabolic pathways associated with meat and wool productivity, reproduction, and resistance to various diseases [19, 20]. To date, complete sequencing of the genome of the domestic rabbit has been performed (https://www.ncbi.nlm.nih.gov/assembly/GCF_000003625.3#/def, the reference genome deposited in NCBI GenBank), the whole genome sequences of domestic and wild rabbits have been compared, single nucleotide polymorphisms (SNPs) have been revealed, and genomic regions with polymorphisms associated with the variability of phenotypic characteristics have been identified and described [21, 22].

Taxonomy of the domestic rabbit. Rabbits and hares belong to class *Mammalia* Linnaeus, 1758 (mammals), the order *Lagomorph* Brandt, 1855 (hare-like) (91 living species in total), divided into two families, *Ochotonidae* Thomas, 1897 (pikas) and *Leporidae* Fischer, 1817 (hares, rabbits) [23], which evolved at the border of the Cretaceous and Paleogene periods about 53 million years ago and are in the same main group of mammals as rodents and primates [24]. The specific features of organs and body systems are the basis for dividing rabbits and hares into two very similar externally, but separate species. The karyotype ($2n$) in these two species is different, i.e. 44 chromosomes in rabbits and 48 chromosomes in hares [25-28].

The history of the origin of the domestic rabbit. It is assumed that the domestication of rabbits is began about 12 thousand years ago [29]. The Romans were the first to documentarily record the wild ancestors of the domestic rabbit, involved in domestication from a geographically limited population of the Iberian Peninsula and southwestern France. Archaeological data show that rabbits were widely used in these areas during the Paleolithic, Mesolithic and early Neolithic periods [30, 31].

There is historical evidence that rabbits were the first animals to be kept in captivity in large enclosures for meat production in the Iberian Peninsula during the Roman occupation in the 1st century BC [32]. Marcus Terentius Varro, Roman encyclopedic scholar and writer of the 1st century BC, kept rabbits together with hares in leporaria, the cages for keeping wild animals [33] and fattened them before slaughter [34], but this form of keeping did not significantly affect the behavioral characteristics of animals [35].

Historical records suggest that directed breeding of rabbits probably began around AD 600 in French monasteries by the decree of Pope Gregory I the Great (Gregorius PP. I), who argued that the carcasses of newborn rabbits should not

be implied as meat, so could be eaten during fasting [11, 32, 36]. Later, numerous errors in the citation of the late 6th century manuscript written in Latin were revealed. Thus, the idea that rabbit meat was popular during the fast is not documented [37].

It is known that rabbits were deliberately brought to Europe in the middle of the 10th century, since even then their meat was considered a delicacy [36]. The first morphological changes in the skeleton, involving occipital bones, xiphoid processes of the sternum, acromion of the scapula, coincide with the early data on rabbits as domestic animals in the 18th century [36].

Domestication of rabbits, like other species, was the result of a continuous dynamic process that reflects gradual interactions between humans and animals [38]. It is necessary to consider domestication and associated biological changes as a single process [3]. It includes the relationship between humans and domesticated animals with spatial and temporal transformations of these relationships, including the intensity of the pressure of artificial selection, which entails both changes in the genetic structure and the emergence of new morphological forms. Rabbits were hunted in the II millennium BC, placed in Roman leporaria, transported to the Mediterranean islands, kept in artificial conditions, and reproduced upon cage keeping. As a result, it was only in the 18th century that rabbits acquired the first phenotypic traits of domesticated ones, distinguishing these individuals from wild ones, and were first used as domestic animals. None of the listed stages can be classified as a special “step” of domestication, but in aggregate they formed in rabbits a complex of traits corresponding to domestic animals [37].

From the beginning of the 9th century, thanks to Phoenician traders in the Mediterranean (Fertile Crescent), the global distribution of rabbits as domestic animals bred for meat and skins began. Later (in the Middle Ages) rabbits were brought to the British and other islands of the northeastern Atlantic Ocean, as well as to Australia, Chili, New Zealand, North and South Africa.

Modern rabbit breeds are characterized by a wide phenotypic diversity associated with complex molecular genetic mechanisms [11]. Domestic rabbits differ significantly from wild ancestors and have many morphological variations in body weight, constitution, quality and color of the hairline, ear length, skull structure, changes in the size of the brain, etc., as well as in behavioral traits such as reducing the level of fear and aggressiveness [39].

Morphological and anatomical differences between domesticated rabbit and wild ancestor. Domesticated forms of rabbits differ from their wild ancestor in the morphology of the occipital bones, the xiphoid process of the sternum, the acromion of the shoulder blades, vertebrae (the processes are more branched and thickened), the lower jaw, and the position of the auditory meatus in rabbits with one drooping ear (half-lop rabbits). The ratio for live weight of wild and domesticated rabbits is 1:2.17, for body length 1:1.41, and for skull volume 1:1.15. Thus, the size of the skull and, consequently, the brain, as shown by body measurements in wild and domestic individuals, increased insignificantly, which is explained by the small width of the skull relative to its length in all domestic rabbits. Domesticated species are characterized by the absence of pronounced tubercles and roughness on the bones in the places of muscle attachment, which is due to a general weakening of the muscles [40].

With an increase in body size in rabbits, changes in the cervical vertebrae occurs, that is, the third vertebra, due to the development of the transverse processes, becomes similar to the fourth, which, in turn, approaches the fifth vertebra [40].

Morphogenetic processes and morphological differences. The skull, given its complex structure already during embryonic development

(neu-ral crest, pharyngeal arch, dermatocranium, and endocranium), the most informa-tively characterizes morphological diversity [40, 41]. In evolutionary time scales, the total number of heterochronous events (i.e. occurring unevenly with a temporal discrepancy) which lead to changes in the size, shape and functions of organs is large in a dog, cat, domestic horse, sheep, llama, and rabbit [42]. Since morphological transformations during the transition from a wild ancestor to a domesticated form are mediated events, involve, in particular, some species-specific processes, and can be manifested with varying intensity, the established general anatomical features characteristic of domestic animals should not be recognized as a “domestication syndrome” [43]. The species-specific structure of the skull and the change in its proportions during growth is probably one of the most important factors providing morphological diversity [44].

Non-isometric (or allometric) growth forms the potential for morphological variability [45], since even with minor changes in body size it leads to different proportions in animals [46]. In contrast, isometric growth means that two individuals of different sizes tend to be similar in body proportions. The difference in the skull sizes of rabbits domesticated in the Middle Ages [32] has not been quantitatively determined, but their skulls differ significantly phenotypically [11]. The height of the coronal suture indicates a positive allometry in all studied individuals, which is presumably associated with accelerated growth in the postnatal period. Hence, it follows that the domestication syndrome for a rabbit is apparently characteristic only during embryogenesis [47].

Comparative morphometry of wild (*Oryctolagus cuniculus* L.) and domesticated (*Oryctolagus cuniculus* var. *domestica* L.) rabbits ($M \pm SEM$) [48]

Species	Live weight, kg	Brain volume, ml	Amygdala reduction, %	Medial frontal cortex volume, %
Domestic rabbit	4.12±0.25	9.55±0.35	10.1	12.1
Wild ancestor	1.07±0.04	7.98±0.26	8.7	11.1

The proportion of brain volume to the skull size in domestic animals compared to their wild ancestors was found to decrease [48]. So, in spite of the large live weight of domestic rabbits as compared to wild ones (Table), they have a slightly larger absolute brain size (see Table), the contraction of the right and left amygdala in the domesticated rabbit is greater, the volume of the right and left medial frontal cortex increases. This may be one of the factors reducing fear and aggressiveness towards humans in domesticated species, since a decrease in the size of the amygdala with a relative increase in the medial prefrontal cortex in domestic animals, including rabbits, compared to wild individuals, entails changes of unconditioned reflex behavior [49, 50]). For example, in rabbits adapted to life in captivity and to close contact with humans, the manifestation of the protective reflex is reduced and mediated by the absence of the need for the “fight or flight” response [51].

Data on the average size of the skull and dental arches indicate that the skull of wild rabbits is somewhat wider and shorter than that of domestic rabbits. Domestic rabbits have a relatively long skull with a nasal bone protruding forward above the incisors, while wild rabbits have a relatively short skull and nasal bone. Elongation of the roots of incisors and diseases such as periodontal disease are more often observed in domestic rabbits [52-54]. Radiographs reveal relatively high crowns in domestic rabbits as compared to wild animals, which is due to the different diets [55, 56] and, possibly, also depends on anthropogenic factors affecting the animals [55]. Teeth with long crowns and short roots are compensated for by intense abrasion during food intake, typical of rodents, and are considered as an evolutionary adaptation to the high rigidity (abrasiveness) of plants due to

the increased content of silica characteristic of phytoliths in herbs [52, 57-59].

In a domestic rabbit, there is a displacement of the points of muscle attachment, for example, the position of the occipital tubercle. The antegonial notch of the mandible is located on a vertical line relative to the last molars in wild rabbits, while in domestic rabbits it is located behind. The diastema between the two anterior incisors is also affected by changes in the shape of the skull. The evolution of the skull and lower jaw in rabbits was regulated by ecological adaptation [60], including locomotion (movement of animals in space due to their active actions) [61] and types of nutrition [62, 63]. Constant wear of teeth with long crowns and short roots is mainly associated with abrasive nutrition due to the increased amounts of lignin, cellulose, and hard silicate phytoliths in grasses and other plants [64]. The ramus of the lower jaw is higher relative to the position of the angular process, which is displaced dorsally, which leads to a decrease in the distance between the joints of the jaw and the muscles of the angular process (deep and superficial musculus masseter) in domestic rabbits compared to wild ones [65]. The part of the lower jaw that lies ventral-caudal to the notch of the lower jaw (reaches the end of the posterior dorsal point of the angular process) is more pronounced in domestic rabbits than in their wild ancestors. Wild rabbits differ from domestic rabbits by highly developed jaw muscles and increased bite force, which is provided by a shorter skull length and vertically located jaw muscles, while in an elongated skull the muscles are located at an angle and the bite force decreases [66]. Due to the consumption of large amounts of hay by rabbits [67], retrograde lengthening of the tooth root occurs, which leads to various pathological processes and a decrease in appetite [68, 69].

Diversity of the intestinal microbiota of wild and domesticated rabbits. The development of the mammalian gut microbiota begins with the colonization of the sterile gastrointestinal tract of a newborn animal with bacteria through vertical transfer from mother to offspring [70]. Bifidobacteria play a key role in various biological processes, such as suppression of putrefactive and pathogenic microorganisms, as well as the capability of carbohydrate digestion [71].

Bifidobacterium longum and *Bifidobacterium adolescentis* are present in 95.5 and 91.0% of all mammalian species, *Bifidobacterium pseudolongum* and *Bifidobacterium bifidum* in 85.0%. It was found that bifidobacterial biodiversity, including the abundance in the microbiome of species *B. magnum*, *B. bifidum*, *B. boum*, *B. mongoliense*, *B. new_taxa_10*, *B. new_taxa_50*, *B. new_taxa_23*, *B. new_taxa_59*, *B. new_taxa_54* [72], is higher in domesticated species than in wild ones, which confirms the hypothesis that contact with humans, life in captivity, and pressure of artificial selection contribute to the acquisition of new bifidobacterial taxa by mammals.

In wild rabbits, 58 different types of microbiome have been characterized [72], which differ from those in domesticated ones. The feeding habits of wild rabbits are largely determined by their area [73], the availability of forage resources, pressure from predators and population density. Herbs with a high content of structural polysaccharides are the main food for them [74].

Enzymatic profiles, abundance and diversity of gut bacterial community of wild and domestic rabbits have significant differences, e.g. the pH of the cecum content in wild rabbits is more acidic, the ammonia content is lower, and the level of volatile fatty acids is higher compared to those of domestic rabbits [75].

Valeric acid produced by the gut microbiome is found in 87% of domestic rabbits and only in 68% of wild rabbits. The presence of isobutyrate and isovaleric acid is characteristic only of wild rabbits, and is detected in only 25% of animals. Despite the fact that the molar fraction of acetates in wild rabbits is lower, the

proportion of butyrates is higher compared to domesticated rabbits [75].

The amount of soluble fiber in the diet of domestic rabbits is known to influence the bacterial diversity [75]. Bacterial profiles differ not only between wild and domestic animals, but also between groups with a different type of diet, i.e. with low and high levels of soluble fiber. Differences in the abundance of bacteria in domestic rabbits depend on the proportion of soluble fiber in the diet, i.e. a large intake of easily digestible substances into the cecum promotes the reproduction of bacteria) [76, 77]. In wild individuals, dry matter assimilates by better than in domesticated rabbits (58 and 37 g of dry matter per 1 kg of live weight, respectively, or by 55%) [78].

Genetic modifications in the course of domestication. As noted above, the European rabbit (*O. cuniculus*) is the only recognized ancestor of domestic rabbits. This species is widespread in the Iberian Peninsula, where about 1.8 million years ago it diverged into two subspecies, the *O. cuniculus algirus* which lived in the southwestern part of the Iberian Peninsula, and *O. cuniculus cuniculus* which area included the northeast of the Iberian Peninsula and France [21].

Despite the fact that secondary contact in the Pleistocene led to the genetic similarity of both subspecies, *O. c. algirus* and *O. page. cuniculus* retain pronounced distinctions [79]. There are significant differences in the polymorphism of chromosome X regions in the pericentromeric region and distal regions adjacent to the telomeres. It is assumed that the pericentromeric region of the X chromosome that can be involved in the determination of reproductive isolation between the two subspecies [80].

It is known that the level of intrabreed and species genetic polymorphism for some DNA markers in rabbits is 0.2% [9], whereas the modern rabbit differs from its wild ancestor by 60%. Rabbit breeds are relatively young, the coefficient of inbreeding of subpopulations relative to the entire population (correlation between randomly selected gametes within the subpopulation, F_{ST}) [81] is 17.9%. This suggests that rabbits which were the predecessors of the breeds constituted the closed gene pools, which contributed to the accumulation population genetic differences in breeds [21]. A retrospective analysis of population genetic processes shows [82] that the initial population of rabbits involved in domestication numbered less than 1200 individuals [9].

The changes found in structural genes, e.g. *GPC3* (<https://www.genecards.org/cgi-bin/carddisp.pl?gene=GPC3>) and *GPC4* (<https://www.genecards.org/cgi-bin/carddisp.pl?gene=GPC4>), encoding proteins Glypican-3 and Glypican-4 involved in the control of cell division, indicate the effect of artificial selection [83, 84]. The gene networks involved in the control of cell division, including the *GPC3* and *GPC4* genes, can be an indirect target of selection, since body size has historically been the first selectable trait in rabbits [32].

The domestication of the rabbit, as per the available data on the haplotypes of the mitochondrial DNA D-loop, apparently caused a noticeable loss of genetic diversity, as in most domesticated species. The bottleneck effect is a common feature of domestication leading to a decrease in genetic variability in mitochondrial DNA, which correlates with a decrease in selection efficiency [85]. There is a constant decrease in genetic variability at microsatellite loci, mitochondrial DNA and the gene encoding the transcription factor (Sex-Determining Region Y Protein, *SRY*) (<https://www.genecards.org/cgi-bin/carddisp.pl?gene=SRY>, 86), which is probably due to the small populations of rabbits historically bred in isolation [9]. The domestic rabbit is characterized by increased expression of genes *sox6* (transcriptional regulation factor SOX6) (<https://www.genecards.org/cgi-bin/carddisp.pl?gene=SOX6>), as well as *prom1* (Prominin 1) (<https://www.ge->

ncards.org/cgi-bin/carddisp.pl?gene=PROM1&keywords=PROM1) encoding the CD133 antigen. These two genes are involved in modulation of brain development, and their expression levels were higher in domesticated species [87].

Some of the known genetic processes associated with domestication and phenotype occur in the same genes in different types of domestic animals. For example, a certain coat color in dogs [88], pigs [89], horses [90], and feathers in chickens [91] is associated with mutations in the gene encoding the agouti-melanocortin 1 receptor (MC1R) [92]. In laboratory mouse strains, a mutation in the promoter region of *ASIP* (Agouti Signaling Protein) gene was found which is associated with a retroviral insert and leads to the appearance of a black-brown phenotype. In rabbits, it is believed that there are three *ASIP* alleles, including the *at* allele which determines the black-brown coat color [93].

In domestic rabbits, an increased expression is typical for Periplakin (PPL) (cytoskeleton-associated protein) [94], with a decreased expression for myosin 5C (MYO5C, a fibrillar protein, one of the main components of contractile fibers of muscle tissue) [95]. Despite this, changes in the sequences of *cis* elements that regulate the expression of these genes have not been identified [87, 96]. The data on linkage disequilibrium of allelic variants of a number of microsatellites indicate that the values of genetic variability parameters (heterozygosity, proportion of polymorphic loci, genetic distances) in the domestic rabbit are lower than in wild ones [9, 97]. At the same time, for a number of other genomic elements, increased polymorphism is observed. E.g., in some lines of the domestic rabbit, a large number of allelic variants for sperm proteins have been identified [98].

The difference in the expression of some genes in domestic animals and their wild relatives is likely associated with genetic transformations of gene networks, changed predominantly under the influence of artificial selection. In addition, since the earliest genomic studies of domesticated species in comparison with closely related wild species, it has been found that artificial selection involves in reproduction animals with certain characteristics of genes associated with the functions of the immune system [99].

Immunoglobulins (IgG) are a key component of the adaptive immune system, linking antigen recognition to its elimination through several effector functions. IgG is the predominant serum immunoglobulin with a wide spectrum of functional activity, including binding to antigens on the cell surface and interaction with the complement system [100, 101]. The assessment of the genetic diversity of wild populations and domesticated breeds for IgG was previously carried out using serological analysis of their polymorphism using the antigen spectra [102, 103], on the basis of which a high genetic diversity was proved in the populations of Iberian rabbits.

In mammalian genomes, among the dispersed repeats, endogenous retroviruses are widely represented which are derivatives of exogenous viruses that have lost their infectious usefulness, but retained the ability to reproduce through own reverse transcriptase and to move to new genomic regions. Comparison of distribution of endogenous retrovirus (ERV) in domestic rabbit and the ancestral European subspecies, as a rule, indicates the closeness of their origin [21]. Retroviruses integrate a proviral copy of DNA into the host germ line and are thus inherited [104]. ERVs are identified in the host genomes by their similarity to the sequences of exogenous retroviruses of the same genus [105]. The presence and movement of ERVs in the host genome leads to a rearrangement of genomic sequences, which, in particular, promotes the formation of recombinants of endogenous retroviruses, as well as the preservation of specific retroviral regions, for example, single long terminal repeats (Long Terminal Repeats, solo-LTR) [106]. The wide distribution of ERVs in mammalian genomes makes it possible to use

homologous sequences to reconstruct phylogenetic relationships, including for different groups of rabbits [107]. In particular, a comparative genomic analysis of single nucleotide substitutions (SNP) and the distribution of endogenous retroviruses (ERV) in two subspecies of the wild rabbit (French and Spanish, *O. c. cuniculus* and *O. c. algerus*) and in the domestic rabbit revealed a high diversity of ERV in the European rabbit which is due to numerous evolutionary events (domestication, hybridization, and breed formation) [108]. Relatively greater similarity in the ERV distribution was found between the French subspecies and the domestic rabbit compared to the Spanish subspecies. Overall, the wild species has a greater ERV diversity than the domestic rabbit. At the same time, certain ERV families predominantly reproduced in domesticated animals in contrast to the original subspecies.

Molecular methods give new tools in animal husbandry, which make it possible to quickly and accurately identify animals, as well as assess their consolidation and population genetic features of formation; the uniqueness of gene polymorphism and ERV distribution can contribute to the development of methods for managing genetic resources [109].

So, the domestic rabbit is widely used for various agricultural and biomedical purposes. In addition, it is one of the rare examples of a domesticated species living concurrently with an ancestral wild species, which opens up unique opportunities for researching the domestication processes and the “domestication syndrome” common for species from remote taxa. Managing the genetic resources of this unique species depends on clarification of the phenotypic, population genetic and other biological parameters that distinguish the domestic rabbit from the ancestral European subspecies. The comparative analysis allowed identification of a number of phenotypic characteristics that differentiate the domestic rabbit from the ancestral species. We also highlighted a group of genomic DNA markers as a tool for animal identification and gene pool consolidation in order to control genetic resources and to involve valuable donors in breeding based on the modern methods. The revealed patterns can be extended to other domestic animals, which is necessary both in biomedical research and in addressing the problems of food production and processing.

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