The epigenetic role in behavioural adaptation of domestic rabbits

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Abstract. Epigenetics, a subfield of Genetics, provides a mechanistic framework for understanding how gene expression is modulated without altering the DNA sequence, primarily through processes such as DNA methylation, histone modifications, and non-coding RNAs. This mini-review synthesizes current knowledge on the role of epigenetic regulation in the behavioural adaptation of domestic rabbits (*Oryctolagus cuniculus*), with particular emphasis on domestication-driven changes in neural function, stress responsiveness, and social behaviour. Evidence from genomic and transcriptomic studies indicates that rabbit domestication has largely targeted regulatory regions associated with brain development and function, rather than coding sequences. Comparative analyses reveal differential gene expression patterns in key brain regions such as the amygdala and hippocampus, implicating dopaminergic signalling and neuronal structural pathways in the evolution of tameness. Furthermore, environmental stressors—including housing conditions, maternal stress, parasitism, and human interaction—are shown to influence behavioural phenotypes that are likely mediated by epigenetic mechanisms. Although direct epigenetic data in rabbits remain limited, extensive evidence from other domesticated and model species supports the role of epigenetic processes as intermediaries between environmental stimuli and long-term behavioural outcomes. Collectively, these findings position epigenetic regulation as a central component in the behavioural plasticity and adaptive responses of domestic rabbits.
Key Words: epigenetics, domestication, behavioural adaptation, rabbits, gene expression, DNA methylation, stress response, neurobiology, animal welfare, phenotypic plasticity.

Introduction. Epigenetics is a field within Genetics that examines how gene activity and expression are regulated by reversible, heritable changes that do not alter the underlying DNA sequence, focusing on mechanisms such as DNA methylation, histone modification, and non-coding RNAs, and how these processes are influenced by environmental factors, development, and lifestyle, ultimately affecting how cells function and how traits may be expressed across generations (Chrenek et al 2011; Pricop & Pricop 2011; Tikoo et al 2015; Bouchereau et al 2022; Chen et al 2022; Jiang 2024; Gao et al 2025).

Domestication of the European rabbit has produced marked changes in morphology, physiology and especially behaviour, particularly increased tameness and altered social and maternal responses (Petrescu-Mag et al 2012; Carneiro et al 2014; Petrescu-Mag et al 2019; Sato et al 2020; Petrescu-Mag et al 2020; Shchukina et al 2020; Dăescu & Oroian 2024). A growing body of work on domesticated animals and model species shows that epigenetic mechanisms regulating gene expression provide a crucial interface between environmental conditions and behavioural adaptation, and these concepts can be applied to understand behavioural change in domestic rabbits (Jensen 2014; Jensen 2015; Wang et al 2017; Bélteky et al 2018; Sajjanar et al 2025).

The aim of this mini-review is to critically examine and integrate current evidence regarding the role of epigenetic mechanisms in shaping behavioural adaptation in domestic rabbits, with a focus on how gene regulation, environmental factors, and domestication processes interact to influence neural function, stress responsiveness, and behavioural phenotypes.

Epigenetic regulation of brain function and tameness in rabbits and other species. Genome and transcriptome studies in rabbits demonstrate that domestication has mainly targeted gene regulation, with sequence variants enriched in conserved noncoding regions near genes involved in brain and neuronal development (Carneiro et al 2014). Brain RNA-seq in wild versus domestic rabbits revealed hundreds of differentially expressed genes across amygdala, hypothalamus, hippocampus and cortex, despite a short domestication history (Sato et al 2020). In the amygdala, genes associated with dopaminergic function were enriched and consistently upregulated in domestic rabbits, suggesting that altered dopamine signalling contributed to the evolution of tameness (Sato et al 2020). In the hippocampus, genes related to ciliary function were enriched and downregulated in domestic animals, indicating modified neuronal and cerebrospinal fluid-related processes in the domesticated brain (Sato et al 2020). More broadly, comparisons across dogs, pigs and rabbits show relatively few differentially expressed cortical genes between wild and domestic forms, and little overlap among species, implying that domestication-related behavioural traits depend on species-specific regulatory shifts rather than a universal "domestication gene set" (Albert et al 2012).

Epigenetic control of gene expression is increasingly recognised as a major substrate for behavioural evolution under domestication. Work in birds closely linked to domestication contexts shows that selection for reduced fear of humans can, within only five generations, produce clearly divergent DNA methylation patterns in the hypothalamus, affecting genes in metabolic and signalling pathways and paralleling gene expression differences in the same tissue (Bélteky et al 2018). More general reviews on domestication propose that behaviour is particularly sensitive to changes in gene expression, and that epigenetic regulation, especially DNA methylation in regulatory regions, is a key mediator between selection pressures, neural gene expression and behavioural phenotypes such as tameness, sociality and stress responsiveness (Jensen 2014; Jensen 2015).

At the mechanistic level, behaviour-related epigenetic marks link environmental signals, steroid hormones and neural circuits. Stress in different life phases, including prenatal periods, can modify DNA methylation and histone chemistry in brain regions controlling the hypothalamic–pituitary–adrenal (HPA) axis and emotional reactivity, inducing long-term shifts in behaviour and stress sensitivity, sometimes persisting across generations (Jensen 2014; Wang et al 2017). Early life stress in mammals is associated with cell-type-specific epigenetic modifications in neurons and glia that help explain stable individual differences in vulnerability to neuropsychiatric phenotypes (Rahman & McGowan 2022). Such findings provide a conceptual framework for interpreting how selection and captive environments could reshape epigenetic landscapes in rabbit brain regions involved in fear, social behaviour and maternal care.

Environmental stress, epigenetics and behavioural plasticity in domestic animals. Domestic animals routinely experience environmental challenges – thermal extremes, nutritional fluctuations, social regrouping, parasites and human handling – that trigger stress responses and adaptive changes in behaviour (Braconnier et al 2020; Arjona-Jiménez et al 2024; Sajjanar et al 2025). Epigenetic mechanisms are highlighted as central gene-regulatory systems that connect such environmental factors to neuro-endocrine and cellular signalling, enabling both dynamic (reversible) and developmentally stable changes in gene expression that can act as "molecular memories" across the life course and even across generations (Jensen 2014; Wang et al 2017; Sajjanar et al 2025).

Reviews focused on livestock emphasise that epigenetic regulation likely participated in the domestication process itself, facilitating adaptation to captive environments by modulating stress physiology, learning and coping styles. Stable epigenetic modifications are discussed as a mechanistic basis for foetal programming strategies, for example prenatal thermal conditioning or nutritional interventions, that shape later stress resilience and performance in domestic animals (Sajjanar et al 2025). Parallel work in behaviour epigenetics shows that acute and chronic stress can induce transgenerationally stable changes in brain gene expression, HPA-axis sensitivity and behaviour in birds, implying that selection can act on epigenetically mediated phenotypic variation in domestication contexts (Jensen 2014).

In rabbits, several studies illustrate how environmental and physiological stressors shape behaviour and thus create potential selective contexts for epigenetic adaptation. Elevated cortisol around parturition in captive does disrupts progesterone-regulated nest-building, leading to delays in nest construction, smaller litters and higher offspring mortality, with impaired maternal behaviour inferred as the key factor (Benedek et al 2021). Group-housing systems, while ethically desirable for a social species, can provoke agonistic interactions; varying regrouping schedules and seasonal conditions alter the frequency of fights and lesions, revealing strong context- and individual-dependent social stress responses (Braconnier et al 2020). Parasitic infestation combined with obesity in rabbit does reduces locomotor, exploratory and social chinning behaviours and severely compromises reproductive performance and offspring survival, demonstrating that combined chronic stressors can greatly magnify behavioural and physiological disruption (Arjona-Jiménez et al 2024). Although these rabbit studies do not directly measure epigenetic marks, they document robust, stress-responsive behavioural phenotypes in domesticated populations that are precisely the kinds of traits shown in other species to be under epigenetic control (Jensen 2014; Wang et al 2017; Rahman & McGowan 2022; Sajjanar et al 2025).

Human–animal relationships also modulate behavioural adaptation in domestic rabbits. Positive interactions, including gentle handling and food provision, make rabbits more likely to approach humans, accept stroking and show "Affectionate/Interested" emotional descriptors, whereas more distant treatment and simpler environments are associated with more "Indifferent" responses (Fetiveau et al 2024). Given the established links in other taxa between social experience, epigenetic modification of neural circuits and long-term behaviour, such findings in rabbits suggest a plausible role for environmentally shaped epigenetic mechanisms in fine-tuning human-directed sociability in captivity (Jensen 2014; Jensen 2015; Wang et al 2017; Rahman & McGowan 2022).

Epigenetic concepts relevant to behavioural adaptation. A central theme in modern domestication biology is that classical DNA sequence mutations alone cannot explain the breadth and speed of phenotypic change; epigenetic mechanisms add a further layer of heritable and semi-heritable variation in behavioural traits (Jensen 2014; Jensen 2015; Wang et al 2017). Epigenetics is defined as chemical modification of DNA and associated chromatin, such as cytosine methylation and histone tail modifications, that alters gene expression without changing nucleotide sequence (Jensen 2014). These marks integrate environmental information, for example via stress hormones, and orchestrate genome-wide expression programs in a tissue- and cell-type-specific manner (Jensen 2014; Wang et al 2017; Rahman & McGowan 2022).

Evidence across model organisms and humans shows that parental and even grandparental environments – including nutrition, toxins, social stress and caregiving – can induce epigenetic alterations in germ cells or early embryos that are transmitted across generations, producing sex-specific physiological and behavioural effects in descendants (Wang et al 2017). In chickens and other domesticated species, chronic or brief stress exposures can cause inherited changes in brain gene expression and behaviour, indicating that epigenetic variation itself is a substrate on which domestication-related selection can act (Jensen 2014; Jensen 2015; Bélteky et al 2018). This framework can be extrapolated to domestic rabbits, where selection for reduced fear, improved maternal care under captive conditions, and tolerance of human contact could progressively stabilise beneficial epigenetic configurations in neural and endocrine systems.

Rabbit domestication, regulatory variation and behaviour. Genomic studies establish domestic rabbits as an especially informative model for domestication, since the domesticated form (Oryctolagus cuniculus var. domestica) still co-exists with its wild ancestor in Europe, allowing direct comparison of genetic and phenotypic divergence (Carneiro et al 2014; Shchukina et al 2020). Whole-genome analysis reveals more than 100 selective sweeps specific to domestic rabbits, yet only a small number of fixed or nearly fixed SNPs, with the strongest allele-frequency shifts concentrated in conserved noncoding regions near genes involved in brain and neuronal development (Carneiro et al

2014). This pattern indicates that domestication has primarily acted on polygenic, regulatory variation rather than single major "domestication genes", supporting a model in which tame behaviour evolved through modest frequency changes at many loci influencing neurodevelopment and neural plasticity (Carneiro et al 2014).

A review of rabbit domestication and molecular traits emphasises that numerous phenotypic characteristics differentiate domestic from wild rabbits and that molecular genetic markers, including noncoding regulatory elements, can be used to distinguish domestic stocks from ancestral populations (Shchukina et al 2020). Studies on rabbit hair coat further underline the importance of noncoding RNAs in regulating gene expression in specific tissues, illustrating the broader principle that epigenetic control of transcription is a key determinant of domestication-related traits (Dorożyńska & Maj 2020). While these works focus on morphology and production, they confirm that domestic rabbits possess rich, functionally important regulatory variation likely to extend to brain and behaviour.

At the transcriptomic level, comparative work in frontal cortex across dogs, pigs, rabbits and other taxa reveals that domestication generally alters expression of fewer than 1% of genes, with limited overlap among species, suggesting that behavioural domestication is largely species-specific in its molecular underpinnings (Albert et al 2012). Nonetheless, some shared tendencies emerge, such as upregulation of developmental modulators like SOX6 and PROM1 in domestic forms, hinting at convergent shifts in neural developmental programs that may influence behavioural traits such as fear and sociality (Albert et al 2012). In rabbits, the detailed regional transcriptomic analysis showing enhanced dopaminergic gene expression in the amygdala of domestic animals, coupled with downregulation of ciliary genes in hippocampus, provides more direct evidence that domestication has reshaped signalling and structural pathways critical for emotional learning, threat processing and possibly spatial and social cognition (Sato et al 2020).

Examples of epigenetic and regulatory processes with behavioural relevance. Although not centred on behaviour, recent epigenomic work in rabbit brown adipose tissue illustrates the depth of regulatory annotation now possible in this species. Genome-wide mapping of H3K27ac – a histone mark associated with active enhancers – in rabbit brown versus white adipose tissue identified over 130,000 peaks and characterised strongly activated enhancers near key thermogenic genes, some of which are conserved between rabbits and humans. Variants within these regulatory regions contribute to breed differentiation, underscoring how epigenetically marked cis-regulatory elements can be targets of selection (Du et al 2025). Analogous approaches applied to rabbit brain would likely reveal enhancer landscapes underlying domestication-related behavioural traits, including tameness and stress coping.

In birds selected for divergent fear of humans, hypothalamic DNA methylation differences arise rapidly and track with selection direction, affecting genes in signalling and metabolic pathways (Bélteky et al 2018). This demonstrates that selection on a behavioural trait closely analogous to rabbit tameness can produce stable, tissue-specific epigenetic divergence within a few generations. Behaviour epigenetics more broadly shows that stress can act via steroid hormones to change methylation and histone marks in neural promoters, leading to altered gene expression and long-term modifications of fearfulness, exploratory behaviour and HPA-axis activity, with some of these changes transmitted to offspring (Jensen 2014; Wang et al 2017). Such mechanisms provide a biologically plausible route by which the captive environment, including human handling, group housing and early maternal conditions, could shape epigenetic profiles and thereby behaviour in domestic rabbits over both individual lifetimes and across generations.

Behavioural adaptation in domestic rabbits as an epigenetically modulated process. Behavioural ecology and welfare studies in rabbits outline several key behavioural domains that have been reshaped under domestication and captivity, each potentially influenced by epigenetic regulation. Maternal nesting behaviour in domestic does, which is essential for offspring survival, is highly sensitive to hormonal and stress-axis modulation (Benedek et al 2021). The finely coordinated interactions between maternal nest construction, deposition of faecal pellets, and pups' progressive nibbling of hay and maternal faeces support successful transition to solid food and prevent digestive pathology and mortality (Benedek et al 2021; Barrios-Montiel et al 2025). Disruption of this system by elevated cortisol or inappropriate environmental management leads to impaired maternal behaviour and poor offspring outcomes, creating selection pressures for stress-resilient, well-regulated maternal responses in domestic populations (Benedek et al 2021; Barrios-Montiel et al 2025).

Social and human-directed behaviours also differ between wild and domestic rabbits and are central to welfare in farming, pet and experimental contexts (González-Redondo et al 2015; Braconnier et al 2020; Ellis 2020; Fetiveau et al 2024). Domestic rabbits display a range of consistent personality traits, including boldness, exploration and variable responses to humans, which can be reliably measured and are used by caretakers to optimise housing and rehoming (Ellis 2020). Positive human–animal relationships foster more affiliative, less fearful behaviour, facilitating management and potentially improving health (Fetiveau et al 2024). Given extensive evidence from other species that such social and environmental experiences leave epigenetic marks in neural circuits, it is reasonable to interpret rabbit behavioural adaptation in captivity as being at least partly mediated by environmentally responsive epigenetic regulation superimposed on domestication-derived genetic and regulatory variation (Jensen 2014; Jensen 2015; Wang et al 2017; Rahman & McGowan 2022; Sajjanar et al 2025) (Table 1).

Table 1

Links between epigenetic/regulatory processes and behaviourally relevant traits

Epigenetic or regulatory focus	*Species / System*	*Behaviourally relevant outcome*	*Citations*
Enrichment of domestication sweeps in conserved noncoding regions near brain development genes	Domestic vs wild rabbits	Polygenic regulatory basis for tame behaviour and altered neural development	Carneiro et al 2014; Shchukina et al 2020
Differential expression of dopaminergic and ciliary genes in amygdala and hippocampus	Domestic vs wild rabbits	Altered dopamine signalling and hippocampal function contributing to tameness	Sato et al 2020
Rapid divergence in hypothalamic DNA methylation under selection for fear of humans	Red junglefowl	Epigenetic modulation of fearfulness, a key domestication trait	Jensen 2015; Bélteky et al 2018
Stress-induced, sometimes transgenerational, epigenetic changes in brain	Mammalian models	Long-term shifts in stress reactivity and behaviour	Jensen 2014; Wang et al 2017; Rahman & McGowan, 2022
Environmental stress and epigenetic regulation in domestication and adaptation	Domestic animals (review)	Improved understanding of stress adaptation and performance via epigenetic mechanisms	Jensen 2014; Jensen 2015; Sajjanar et al 2025

Summarized by Consensus, 2026.

Conclusions. Epigenetic regulation constitutes a key mechanism linking environmental influences to stable, and sometimes heritable, behavioural modifications. In domestic rabbits, available genomic and transcriptomic evidence indicates that domestication has primarily targeted gene regulatory elements rather than coding sequences, particularly those associated with neural development and function. This supports a polygenic regulatory framework in which behavioural traits such as tameness, sociality, and stress responsiveness arise from coordinated shifts in gene expression across multiple loci.

Neurobiological findings, including altered dopaminergic signalling in the amygdala and structural-functional changes in the hippocampus, underscore the importance of regulatory modulation in shaping domestication-related behaviours. These patterns are consistent with broader evidence that behavioural traits are especially sensitive to changes in gene expression.

Environmental stressors play a central role in modulating rabbit behaviour via neuroendocrine pathways such as the HPA axis. Although direct epigenetic data in rabbits remain limited, documented stress-induced behavioural changes strongly imply underlying epigenetic mechanisms, as supported by extensive cross-species research demonstrating persistent and sometimes transgenerational effects of stress on gene regulation and behaviour.

Human–animal interactions further contribute to behavioural adaptation, with positive handling and enriched environments promoting reduced fear and increased sociability. Such effects are likely mediated by experience-dependent modifications in neural regulatory systems.

Understanding these processes has important implications for animal welfare and management, suggesting that environmental optimization and early-life interventions may enhance desirable behavioural traits and stress resilience. Integrating epigenomic approaches into future research will be essential for identifying regulatory markers and clarifying the molecular basis of behavioural adaptation in domestic rabbits.

Conflict of interest. The authors declare that there is no conflict of interest.

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