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Genetic variability of canine *NR3C1* gene and its role in glucocorticoid signaling

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Abstract

The glucocorticoid receptor is a ligand-activated transcription factor that mediates the actions of glucocorticoids and regulates genes involved in metabolism, development, inflammation, and the immune response. Glucocorticoids are lipophilic, allowing them to freely cross cell membranes and bind to glucocorticoid receptors, which, upon translocation to the nucleus, enhance or suppress transcription of target genes. The glucocorticoid receptor is encoded by the *NR3C1* gene, which has been identified in both humans and dogs. This gene is located on canine chromosome 2 and contains nine exons. The *NR3C1* gene encodes multiple glucocorticoid receptor isoforms via alternative splicing and alternative translation initiation, leading to diverse cellular and physiological responses. Previous studies of *NR3C1* gene polymorphisms have been conducted in the context of various human diseases, such as rheumatoid arthritis, multiple sclerosis, and an increased risk of major depression. In dogs, identified polymorphisms have been investigated in relation to immune thrombocytopenia and in clinical studies evaluating dogs' responses to steroid medications. Since glucocorticoids such as cortisol are key mediators of the hypothalamic-pituitary-adrenal (HPA) axis and play a central role in the physiological adaptation to stress, variations in the *NR3C1* gene may influence receptor sensitivity, feedback regulation, and overall stress reactivity in dogs.

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Investigating the occurrence of genetic variants and the relationship between *NR3C1* polymorphisms, cortisol levels, and behavioural indicators of stress may provide valuable insights into canine stress physiology and support the development of more individualized approaches to animal welfare assessment and veterinary treatment. Particular attention should be given to indigenous dog breeds, which represent unique genetic resources shaped by long-term adaptation to specific environmental conditions and management practices, and may therefore harbour distinct genetic variants associated with stress resilience and adaptive capacity.

Keywords: dogs, NR3C1 gene, stress response, corticosteroids, polymorphisms

Introduction

Glucocorticoids are steroid hormones synthesized in the adrenal cortex and are essential for metabolism, immune regulation, development, and stress adaptation. Their biological effects are mediated primarily through the glucocorticoid receptor (GR), a ligand-activated transcription factor encoded by the *NR3C1* gene (*Nuclear Receptor Subfamily 3, Group C, Member 1*) (COSTA et al., 2016). Following hormone binding, the receptor translocates to the nucleus where it regulates transcription of numerous target genes involved in inflammation, metabolism, and homeostasis.

The canine *NR3C1* gene is located on chromosome 2 and contains nine exons. Similar to humans, alternative splicing and alternative promoter usage generate multiple receptor isoforms that may differ in biological activity (VANDEVYVER et al., 2014). Studies in human medicine have demonstrated associations between *NR3C1* polymorphisms and diseases such as rheumatoid arthritis, multiple sclerosis, depression, and altered responses to glucocorticoid therapy (TAYLER et al., 2022). Comparable investigations in dogs remain limited but indicate that genetic variation may affect corticosteroid sensitivity and immune-mediated diseases.

Because cortisol is the primary glucocorticoid involved in the hypothalamic-pituitary-adrenal (HPA) axis regulation, variation in receptor structure and expression may influence behavioral and physiological responses to stress. Understanding canine *NR3C1* variability may therefore contribute to veterinary medicine, animal welfare research, and breeding strategies aimed at improving stress resilience. Despite these advances, knowledge regarding the functional significance of canine NR3C1 variation remains limited, highlighting the need for further investigation.

Material and methods

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This extended abstract is based on a comprehensive review of published scientific literature addressing glucocorticoid receptor biology, *NR3C1* gene structure, polymorphisms, alternative splicing, cortisol physiology, stress responses, and clinical applications in dogs. Relevant peer-reviewed studies were evaluated and synthesized to provide an integrated overview of current knowledge and future research directions.

Results and discussion

The glucocorticoid receptor belongs to the nuclear receptor superfamily and consists of an N-terminal transactivation domain, a DNA-binding domain, and a ligand-binding domain. Two principal receptor isoforms, GRα and GRβ, have been described. GRα is considered the primary biologically active receptor, whereas GRβ may act as a dominant negative regulator of glucocorticoid signaling (VANDEVYVER et al., 2014).

Activation of the HPA axis during stress results in glucocorticoid secretion, predominantly cortisol. Cortisol concentrations in dogs can be measured in plasma, saliva, urine, feces, and hair (CHMELÍKOVÁ et al, 2020; VAN DER LAAN et al., 2022). Although cortisol is widely used as a biomarker of stress, interpretation requires consideration of individual variation, environmental context, and previous experiences (FERRANS et al., 2025).

COSTA et al. (2016) identified six polymorphisms within the canine *NR3C1* gene, including two nonsynonymous variants predicted to affect receptor function. These findings provided the first evidence that naturally occurring genetic variation may influence glucocorticoid responsiveness in dogs. The same study also demonstrated the existence of multiple transcript variants generated through alternative promoter usage.

Subsequent research has highlighted the clinical relevance of *NR3C1* variation. TAYLER et al. (2022) investigated *NR3C1* polymorphisms in English Cocker Spaniels with primary immune thrombocytopenia and demonstrated breed-specific differences in allele frequencies. Although direct associations with treatment outcomes were not identified, the results supported the hypothesis that *NR3C1* polymorphisms are unevenly distributed among breeds and may contribute to variability in disease susceptibility.

Alternative splicing represents another important mechanism contributing to receptor diversity. KÁLLAI et al. (2021) identified a previously unknown canine ortholog of the GR-P splice variant and reported altered expression patterns in dogs with systemic inflammatory response syndrome (SIRS). These findings suggest that receptor isoforms may influence disease progression and survival.

Studies by YAMANAKA et al. (2019) further demonstrated that structural variation within canine glucocorticoid receptors can alter glucocorticoid sensitivity. Such

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observations are consistent with human studies showing that polymorphisms and receptor abnormalities influence individual responses to endogenous cortisol and therapeutic glucocorticoids.

From an animal welfare perspective, *NR3C1* variation may affect behavioral responses to stress. Cortisol serves as a major mediator of stress adaptation, and prolonged dysregulation of glucocorticoid signaling has been linked to anxiety, altered behavior, immune dysfunction, and reduced welfare (MÂRZA et al., 2024). Recent reviews emphasize that integrating genetic markers with physiological and behavioral indicators may improve assessment of stress resilience in domestic dogs (COBB et al., 2016; KASZYCKA et al., 2025).

Indigenous and locally adapted dog breeds may be particularly valuable in this context. Long-term adaptation to specific environmental conditions may have promoted the accumulation of genetic variants affecting HPA-axis function and glucocorticoid signaling. Characterizing *NR3C1* diversity within these populations could reveal novel adaptive mechanisms and support conservation of unique genetic resources.

Conclusion and recommendation

Current evidence indicates that the canine *NR3C1* gene exhibits considerable genetic and transcriptional variability. Identified polymorphisms and splice variants may influence receptor function, glucocorticoid sensitivity, stress responsiveness, and clinical outcomes. Although canine research remains less extensive than human research, available findings support the importance of *NR3C1* as a candidate gene for studies of animal welfare, stress physiology, and personalized veterinary medicine.

Future investigations should focus on large-scale population studies, genotype-phenotype associations, and the integration of molecular, endocrine, and behavioral data. Particular attention should be directed toward indigenous dog breeds, which may harbor unique genetic variants associated with adaptation and resilience. Such knowledge may contribute to improved welfare assessment, optimized therapeutic protocols, and conservation of valuable canine genetic resources.

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