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The Role of *TLR* Genes in Canid Immunity: Insights from Wolves, Coyotes, and Dogs

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Abstract This study systematically reviews the critical role of Toll-like receptor (TLR) genes in canid immunity, focusing on the genetic polymorphisms, functional mechanisms, and evolutionary dynamics of *TLR* genes in wolves, coyotes, and domestic dogs. As an essential component of the innate immune system, TLRs recognize pathogen-associated molecular patterns (PAMPs) and activate immune signaling pathways, playing a central role in combating bacterial, viral, and fungal pathogens. The diversity of *TLR* genes is closely linked to host immune competence and disease susceptibility, with African wild dogs exhibiting higher TLR polymorphism, potentially enhancing their resistance to canine distemper virus (CDV). This study reveals how specific variations in genes such as TLR2, TLR4, and TLR7 influence immune responses and highlights the importance of pathogen-mediated selection pressures in maintaining genetic diversity. It further explores the potential applications of *TLR* genes in conservation and breeding, including the use of genetic markers for marker-assisted selection to enhance disease resistance in domestic dogs and the management of genetic diversity to address regional pathogen pressures in wild canids. By synthesizing current research findings, this study identifies future research directions, emphasizing the application of genomic and transcriptomic technologies in elucidating the functions and evolution of *TLR* genes.

Keywords Toll-like receptor (TLR); Canid immunity; Genetic diversity; Pathogen resistance; Conservation and breeding

1 Introduction

Canid species, including wolves, coyotes, and domestic dogs, possess a complex and highly adaptive immune system that enables them to combat a wide array of pathogens. The immune system is a complex network of cells, tissues, and organs that work together to defend the body against harmful pathogens and maintain homeostasis (Liu and Huang, 2024). The innate immune system, which serves as the first line of defense, plays a crucial role in recognizing and responding to infectious agents. Among the key components of this system are Toll-like receptors (TLRs), which are essential for detecting microbial infections and initiating immune responses. Understanding the genetic and functional diversity of TLRs in canids is vital for comprehending their immune capabilities and disease susceptibilities.

Toll-like receptors (TLRs) are a family of pattern recognition receptors that identify pathogen-associated molecular patterns (PAMPs) and activate downstream signaling pathways to elicit immune responses. TLRs are pivotal in recognizing a broad spectrum of pathogens, including viruses, bacteria, and fungi. Polymorphisms in *TLR* genes can significantly influence the effectiveness of immune responses and the susceptibility of hosts to various diseases. For instance, variations in TLR2, TLR3, TLR4, TLR7, and TLR8 have been linked to differential susceptibility to canine distemper virus (CDV) in African wild dogs and lions, highlighting the critical role of TLR diversity in disease resistance (Loots et al., 2018). Additionally, TLR polymorphisms have been shown to undergo pathogen-mediated selection, maintaining genetic diversity in natural populations and influencing disease susceptibility (Quéméré et al., 2021).

This study summarizes the genetic variations in *TLR* genes across different canid species, explores the evolutionary pressures shaping TLR diversity in wild populations, evaluates the functional impacts of TLR polymorphisms on immune responses to specific pathogens, and highlights the significance of TLR research in

canid conservation and disease management. It aims to provide comprehensive insights into how these receptors contribute to disease resistance and overall immune competence.

2 *TLR* Genes: Structure and Function

2.1 General overview of *TLR* gene families

Toll-like receptors (TLRs) are a critical component of the innate immune system, serving as pattern recognition receptors (PRRs) that detect pathogen-associated molecular patterns (PAMPs) from various microbes. TLRs are evolutionarily conserved across species, including canids such as wolves, coyotes, and dogs. These receptors are integral in recognizing a wide array of microbial components, including bacterial lipoproteins, lipopolysaccharides, and viral nucleic acids, thereby initiating immune responses (Dolasia et al., 2018; Fitzgerald and Kagan, 2020; Guo et al., 2023). The TLR family is composed of multiple members, each with specific ligand recognition capabilities, such as TLR1, TLR2, TLR4, and TLR5, which are known to recognize bacterial components, and TLR3, TLR7, TLR8, and TLR9, which are involved in viral recognition (Mukherjee et al., 2019; Zhou et al., 2021).

2.2 Mechanisms of action in immune response

Upon recognition of PAMPs, TLRs activate downstream signaling pathways that lead to the production of cytokines and other inflammatory mediators. This process is primarily mediated through adaptor proteins such as MyD88 (myeloid differentiation primary-response protein 88), which forms a complex known as the myddosome. This complex recruits and activates IL-1R-associated kinases (IRAKs), which are crucial for the propagation of the signal leading to the activation of transcription factors like NF-κB and the production of pro-inflammatory cytokines (Guo et al., 2023; Pereira and Gazzinelli, 2023). Additionally, TLRs can form supramolecular organizing centers (SMOCs) that ensure precise and robust signaling responses (Fitzgerald and Kagan, 2020). The activation of TLRs not only triggers immediate innate immune responses but also shapes adaptive immunity by influencing the activation and differentiation of T and B cells (Dolasia et al., 2018).

2.3 Evolutionary perspectives of *TLR* genes in canids

The evolutionary dynamics of *TLR* genes in canids reveal significant polymorphism and adaptive evolution, driven by pathogen-mediated selection. Studies have shown that *TLR* genes exhibit high levels of genetic diversity, similar to the major histocompatibility complex (MHC) genes, which are crucial for adaptive immunity (Těšický et al., 2020; Quéméré et al., 2021). This diversity is maintained through balancing selection, where different alleles confer advantages against various pathogens, thus promoting heterozygosity within populations. For instance, specific TLR polymorphisms have been associated with differential susceptibility to infections, highlighting their role in the evolutionary arms race between hosts and pathogens (Mukherjee et al., 2019; Wang et al., 2021). In canids, the conservation and variation of *TLR* genes suggest a complex interplay between genetic drift, selection pressures, and environmental factors, contributing to the robustness of their immune responses (Těšický et al., 2020; Guo et al., 2023).

3 Comparative Insights Across Canid Species

3.1 *TLR* gene variability in wolves

In North American gray wolves, the *TLR3* gene has been studied in relation to the KB allele, which is associated with black coat color. This allele, introduced through hybridization with dogs, underwent a selective sweep, increasing its frequency in wild wolf populations. Despite this positive selection, wolves with the KBB genotype exhibit lower fitness compared to those with the KyB genotype, suggesting pleiotropic effects of the KB allele on phenotypes beyond coat color. However, studies have shown that the K locus genotype does not predict the transcriptional response to TLR3 pathway stimulation or infection by canine distemper virus (CDV), indicating that the gene expression response does not explain the pleiotropic effects on fitness (Figure 1) (Johnston et al., 2021).

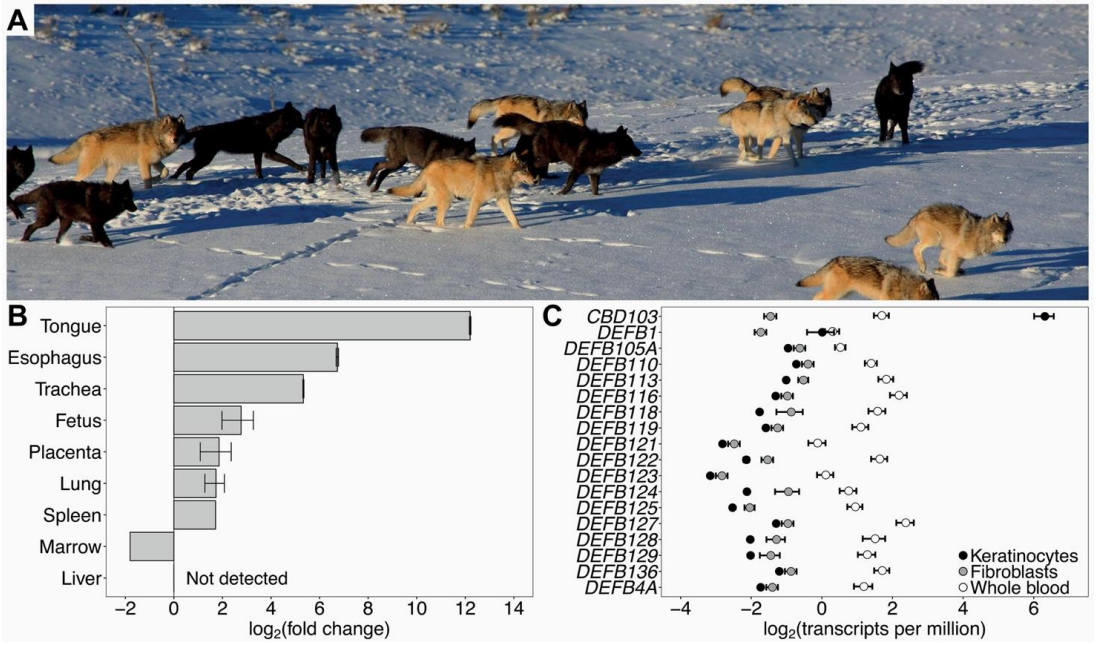

Figure 1 *CBD103* gene expression in North American gray wolves (Adopted from Johnston et al., 2021)

Image caption: (A) Coat color polymorphism in North American gray wolves in Yellowstone National Park, in which coat color can be gray or black (photo credit Dan Stahler/National Park Service photo). Black coat color is dominantly inherited, conferred by a 3 base pair coding deletion in *CBD103*. (B) *CBD103* expression, relative to expression in dog testis, across tissues of a recently deceased pregnant female K^{yy} wolf. Error bars represent standard errors across RT-qPCR replicates (2–3 replicates per tissue). A single tissue sample was collected for each tissue except fetus and placenta, which each represent 2 tissue samples (i.e., from 2 fetuses). (C) Absolute expression of annotated beta defensins in epidermal keratinocytes (N = 23), fibroblasts (N = 6), and whole blood (N = 25) from North American gray wolves. Only *CBD103* is highly expressed in keratinocytes (Adopted from Johnston et al., 2021)

3.2 Functional implications of *TLR* genes in coyotes

While specific studies on *TLR* genes in coyotes are limited, insights can be drawn from related species and general TLR functionality. TLRs play a crucial role in recognizing pathogens and initiating immune responses. For instance, in other wild species, *TLR* genes exhibit significant polymorphism, which is maintained by pathogen-mediated selection. This polymorphism influences disease susceptibility and immune responses, as seen in studies on roe deer where TLR2 polymorphism is shaped by antagonistic selection pressures from different pathogens (Quéméré et al., 2021). Similar mechanisms are likely at play in coyotes, where *TLR* gene variability could influence their ability to respond to diverse pathogen challenges in their environment.

3.3 *TLR* gene adaptations in domestic dogs

Domestic dogs have undergone significant genetic adaptations during domestication, including changes in *TLR* genes. Whole-genome sequencing of African dogs has revealed positive selection in genes linked to immunity, such as ADGRE1, which provides protective host defense against Plasmodium infections. This gene is also associated with severe malaria resistance in humans, highlighting the role of TLR-related genes in adapting to tropical environments (Liu et al., 2018). Additionally, structural variations in the dog genome, including insertions and deletions, have been linked to immune system functions, further illustrating the impact of domestication on *TLR* gene adaptations (Wang et al., 2018).

4 *TLR* Genes and Disease Resistance in Canids

4.1 Role of TLRs in bacterial and viral infections

Toll-like receptors (TLRs) are crucial components of the innate immune system, recognizing pathogen-associated molecular patterns (PAMPs) and initiating immune responses against a variety of pathogens, including bacteria and viruses. TLRs such as TLR2, TLR4, and TLR7 have been shown to play significant roles in the immune

response to infections in canids. For instance, TLR2 is involved in recognizing bacterial lipoproteins, while TLR4 detects lipopolysaccharides from Gram-negative bacteria, and TLR7 is essential for recognizing viral single-stranded RNA (Loots et al., 2018; Mukherjee et al., 2019; Heni et al., 2020). Polymorphisms in these *TLR* genes can influence the host's susceptibility to infections. For example, a study on African wild dogs and lions revealed that TLR2 polymorphisms might affect susceptibility to canine distemper virus (CDV), with specific amino acid changes potentially altering TLR2 function and expression (Loots et al., 2018).

4.2 Case studies: disease susceptibility linked to TLR variants

Several case studies have highlighted the link between *TLR* gene variants and disease susceptibility in canids. In a study of CDV outbreaks in South Africa, non-synonymous single nucleotide polymorphisms (SNPs) in TLR2, TLR3, TLR4, TLR7, and TLR8 were investigated. The study found a higher rate of TLR polymorphisms in African wild dogs compared to lions, with a specific TLR2 variant (Met527Thr) potentially influencing CDV susceptibility in lions (Loots et al., 2018). Another study on roe deer demonstrated that TLR2 polymorphisms are subject to pathogen-mediated selection, affecting susceptibility to infections like Toxoplasma and Chlamydia (Quéméré et al., 2021). These findings underscore the importance of TLR genetic diversity in disease resistance and susceptibility in wildlife.

4.3 Genetic markers and breeding for enhanced immunity

The identification of TLR polymorphisms as genetic markers offers promising avenues for breeding programs aimed at enhancing disease resistance in canids. For example, the presence of specific TLR variants can be used to select individuals with enhanced immune responses for breeding. In dairy cattle, TLR SNPs have been identified as potential markers for breeding strategies to improve resistance to diseases such as mastitis and bovine tuberculosis (Maljković et al., 2023). Similarly, in canids, TLR polymorphisms could be utilized to develop marker-assisted selection programs to enhance disease resistance. The use of retrotransposon insertion polymorphisms (RIPs) in *TLR* genes, such as the 192 bp ERV insertion in TLR6, has shown potential in increasing TLR expression and downstream immune responses, which could be applied in breeding programs for disease-resistant animals (Wang et al., 2021).

5 Case Study

5.1 Regional pathogen pressure in wild and domestic canids

Pathogen pressure varies significantly across regions and species, influencing the genetic diversity of Toll-like receptors (TLRs) in canids. For instance, in South Africa, outbreaks of canine distemper virus (CDV) in lions and African wild dogs revealed different susceptibilities and TLR polymorphisms. Lions exhibited lower TLR diversity compared to African wild dogs, which showed higher rates of polymorphism within TLR loci (Loots et al., 2018). Similarly, in a study on neotropical rodents, TLR4 haplotypes varied across landscapes with different degrees of anthropogenic disturbance, affecting resistance to gastrointestinal nematodes and Hepacivirus (Heni et al., 2020). These findings underscore the importance of regional pathogen pressures in shaping TLR diversity and pathogen resistance in wild and domestic canids.

5.2 Sampling and genotyping of TLR variants

Sampling and genotyping of TLR variants involve collecting tissue or blood samples from canids and analyzing the genetic sequences of *TLR* genes. In the study of CDV outbreaks in South Africa, researchers investigated non-synonymous single nucleotide polymorphisms (SNPs) in the coding regions of TLR2, TLR3, TLR4, TLR7, and TLR8 genes (Loots et al., 2018). Similarly, in a study on porcine *TLR* genes, bioinformatic prediction combined with PCR-based amplification was used to screen for retrotransposon insertion polymorphisms (RIPs) (Wang et al., 2021). These methods allow for the identification of specific TLR variants and their association with disease susceptibility.

5.3 Correlation between TLR variants and pathogen resistance

The correlation between TLR variants and pathogen resistance is evident in several studies. For example, a single amino acid change (Met527Thr) within the leucine-rich repeat of TLR2 was observed in a surviving lioness

during a CDV outbreak, suggesting a potential influence on TLR2 function and CDV resistance (Loots et al., 2018). In neotropical rodents, specific TLR4 haplotypes were associated with different levels of infection by nematodes and Hepacivirus, indicating that TLR4 diversity plays a role in pathogen resistance (Heni et al., 2020). Additionally, polymorphic residues in *TLR* genes, such as I602S (TLR1) and D299G (TLR4), have been linked to differential immune responses in various species (Figure 2) (Mukherjee et al., 2019).

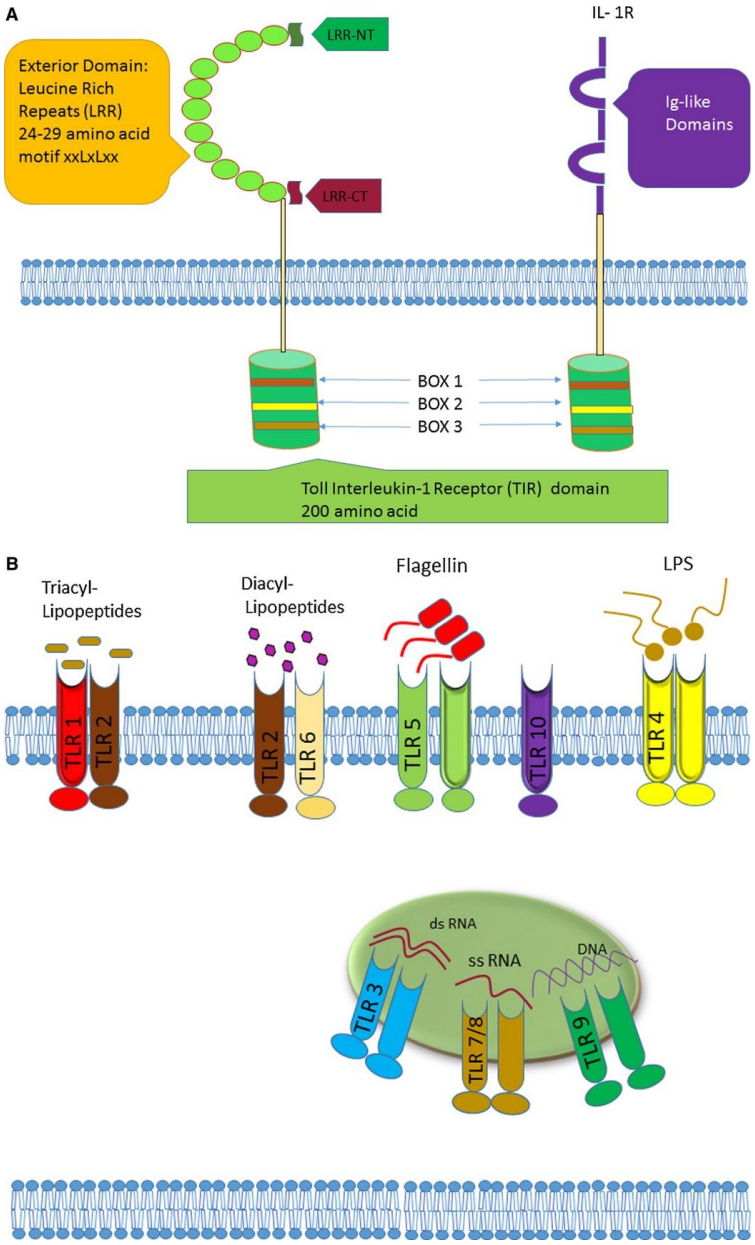

Figure 2 Biochemistry of TLRs (Adopted from Mukherjee et al., 2019)

Image caption: A, Structures and transmembrane domain morphologies of TLR and IL-1 receptor. The existence of LRR motif in the extracellular domain the unique feature of transmembrane TLRs, while the TIR domain is the feature that is homologous to IL-1 receptor. B, Recognition of molecular patterns from different infectious pathogens by TLRs. TLRs (TLR 1, 2, 4, 5, 6, 10) located on the plasma membrane of innate immune cells recognize distinct ligand from invading pathogens. TLR2 in its active form dimerizes either with TLR1 or TLR6 and respectively recognize triacyl- or diacyl-lipopeptide from bacteria. TLR5 senses flagellin protein of invading bacteria, whereas TLR4 binds with LPS moiety of gram-negative bacteria. Intracellular TLRs (TLR 7, 8, 9) generally recognizes patterns of the pathogens those entering in the cell. TLR3 and TLR7/8 respectively detect double (dsRNA) and single-stranded RNA (ssRNA) of viruses. TLR9 selectively recognizes double-stranded DNA of intracellular pathogens. CT, C terminus; Ig, immunoglobulin; IL-1, interleukin-1; LPS, lipopolysaccharide; LRR, leucine-rich repeats; NT, N terminus; TIR, Toll-interleukin-1 receptor domain; TLR, Toll-like receptor (Adopted from Mukherjee et al., 2019)

5.4 Implications for conservation and breeding strategies

Understanding the role of *TLR* genes in pathogen resistance has significant implications for conservation and breeding strategies. For instance, identifying TLR variants associated with disease resistance can inform selective breeding programs aimed at enhancing the immune resilience of domestic canids (Wang et al., 2021). In wildlife conservation, maintaining genetic diversity in *TLR* genes is crucial for the adaptive potential of populations facing diverse pathogen pressures (Quéméré et al., 2021). Moreover, insights into TLR-mediated immunity can guide the development of targeted interventions to mitigate disease outbreaks in both wild and domestic canid populations.

6 Applications of TLR Research in Canid Conservation and Breeding

6.1 Utilizing TLR variants for breeding disease-resistant dogs

Toll-like receptors (TLRs) play a crucial role in the innate immune system by recognizing pathogen-associated molecular patterns (PAMPs) and initiating immune responses. The identification of *TLR* gene polymorphisms has significant implications for breeding disease-resistant dogs. For instance, polymorphisms in *TLR* genes have been associated with varying susceptibility to infectious diseases such as canine distemper virus (CDV) (Loots et al., 2018). By identifying and selecting for beneficial TLR variants, breeders can potentially enhance disease resistance in domestic dogs. This approach is supported by studies in other species, such as cattle, where TLR polymorphisms have been linked to resistance against diseases like mastitis and tuberculosis (Maljković et al., 2023). The application of similar strategies in dogs could lead to the development of breeds with improved health and longevity.

6.2 Conservation implications for wild canids: genetic management

The genetic diversity of *TLR* genes in wild canid populations, such as wolves and coyotes, is essential for their ability to respond to various pathogens. Research has shown that TLR diversity can influence disease susceptibility and overall fitness in wildlife (Heni et al., 2020; Quéméré et al., 2021). For example, in African wild dogs, higher TLR polymorphism rates were observed compared to lions, which may contribute to their differential susceptibility to CDV (Loots et al., 2018). Conservation programs can utilize this information to manage genetic diversity in wild canid populations, ensuring that they maintain a robust immune system capable of adapting to new and emerging diseases. Additionally, understanding the role of *TLR* genes in pathogen resistance can inform reintroduction and translocation efforts, helping to establish healthy and resilient populations in the wild.

6.3 Challenges and future directions

Despite the promising applications of TLR research in canid conservation and breeding, several challenges remain. One major challenge is the complexity of *TLR* gene interactions and their influence on immune responses. While specific TLR polymorphisms have been linked to disease resistance, the overall genetic architecture and environmental factors also play significant roles (Mukherjee et al., 2019). Furthermore, the genetic diversity of TLRs in different canid populations needs to be thoroughly characterized to identify beneficial variants accurately. Future research should focus on large-scale genomic studies to map TLR diversity and its functional implications across various canid species. Additionally, integrating TLR research with other genetic and ecological data will provide a more comprehensive understanding of canid immunity and inform effective conservation and breeding strategies.

7 Concluding Remarks

The investigation into the role of Toll-like receptor (TLR) genes in canid immunity has revealed significant insights into how genetic variations influence susceptibility to pathogens such as the canine distemper virus (CDV). In African wild dogs, a higher rate of polymorphism was observed within TLR loci compared to lions, suggesting a potential link between TLR diversity and immune response variability. Specifically, a notable amino acid change (Met527Thr) in TLR2 was identified in a surviving lioness, indicating that such polymorphisms could affect TLR function and, consequently, host immunity. Additionally, research on North American gray wolves demonstrated that the K locus genotype did not predict the transcriptional response to TLR3 stimulation or CDV

infection, suggesting that other genetic or environmental factors may contribute to the observed fitness differences.

The findings underscore the importance of genetic diversity in the immune response of canids. The higher polymorphism rates in *TLR* genes among African wild dogs may confer a broader range of immune responses, potentially enhancing their resilience to diseases like CDV. This genetic variability is crucial for conservation efforts, as it highlights the need to maintain genetic diversity within populations to ensure robust immune defenses. The study on gray wolves further emphasizes the complexity of genetic influences on immunity, suggesting that conservation strategies should consider both genetic and environmental factors to fully understand and support the health of wild canid populations.

Future research should aim to expand the scope of *TLR* gene studies across different canid species and populations to better understand the evolutionary pressures shaping immune responses. Investigating the functional consequences of specific TLR polymorphisms, such as the Met527Thr change in TLR2, could provide deeper insights into the mechanisms of pathogen resistance. Additionally, exploring the interaction between genetic variations and environmental factors will be crucial in elucidating the complex dynamics of canid immunity. The use of advanced genomic and transcriptomic techniques, as demonstrated in the study of gray wolves, should be further developed to uncover the pleiotropic effects of genetic variations on fitness and disease susceptibility.

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Conflict of Interest Disclosure

The authors affirm that this research was conducted without any commercial or financial relationships that could be construed as a potential conflict of interest.

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