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Digest

Digest: do weakly deleterious mutations exacerbate reproductive and health challenges in species with prolonged bottlenecks?

Aryan Ghader

Department of Biology, University of Western Ontario, London, ON, Canada

Corresponding author: Department of Biology, University of Western Ontario, London, ON, N6A 5B7, Canada. Email: aryanghader@outlook.com
This article corresponds to Peers, J. A., Nash, W. J., Haerty, W. (2025). Gene pseudogenization in fertility-associated genes in cheetah (*Acinonyx jubatus*), a species with long-term low effective population size. *Evolution*, qpaf005. https://doi.org/10.1093/evolut/qpaf005

Abstract

Do weakly deleterious mutations contribute to the reproductive and health challenges of bottlenecked species? Peers et al. (2025. Gene pseudogenization in fertility-associated genes in cheetah (*Acinonyx jubatus*), a species with long-term low effective population size. *Evolution*, qpaf005. doi:10.1093/evolut/qpaf005) investigated the role of prolonged low effective population size in cheetahs (*A. jubatus*) and its implications in the accumulation of pseudogenes. They identified 65 cheetah-specific premature termination codons, and four of which (DEFB116, ARL13A, CFAP119, and NT5DC4) were linked to male fertility and immune deficiencies. These findings reveal how pseudogenization may contribute to fertility challenges and reproductive health decline.

Cheetahs (*A. jubatus*) are known for their speed and agility, yet their evolutionary history is marked by genetic limitations. Historical bottlenecks can reduce effective population size, leading to low genetic diversity and the accumulation of weakly deleterious mutations (Grossen et al., 2020; Peischl et al., 2016). A potential consequence of this genetic erosion is pseudogenization—a process in which functional genes lose their ability to encode proteins due to accumulated mutations (Zhang et al., 2007). This phenomenon may result in inbreeding depression symptoms such as significant reproductive difficulties, weakened immune systems, and a general decline in overall fitness.

In a recent study, Peers et al., (2025) used comparative genomics to explore gene pseudogenization in cheetahs. By analyzing eight felid genomes for species-specific genetic changes, they identified 65 novel cheetah-specific premature termination codons (PTCs). Among these, four genes—DEFB116, ARL13A, CFAP119, and NT5DC4—stood out, as their mutations were conserved in both wild and captive cheetahs, indicating a long-term persistence and a potential role in male fertility issues and immune deficiencies. Unlike previous studies that focused on a single population, Peers et al. (2025) utilized new genomic resources to analyze species-wide genetic changes, providing a more comprehensive picture of pseudogenization in cheetahs. The study emphasizes that while individual mutations may have minor effects, their cumulative impact may significantly undermine cheetah fitness. This phenomenon mirrors other well-documented species bottlenecks, such as that impacting the woolly mammoth. Indeed it is believed that a reduced effective population size for mammoths weakened the ability of natural selection to remove harmful mutations, ultimately contributing to the species' extinction (Rogers & Slatkin, 2017).

One of the most significant findings of this recent study on cheetahs was uncovering PTC in DEFB116, because this beta-defensin family gene is critical for reproductive and respiratory systems. Cheetahs are known to have a compromised immune system due to low genetic diversity, which increases their susceptibility to infections. Given that beta-defensins play a role in respiratory defense, the loss of function in DEFB116 could potentially exacerbate vulnerability to respiratory pathogens (Terio et al., 2018). Similarly, the PTC found in ARL13A and CFAP119, which are involved in sperm development and motility, may help to explain the low sperm count and high levels of abnormal sperm observed in male cheetahs. These genetic vulnerabilities align with longstanding observations of fertility issues in both wild and captive populations, though further research is needed to establish a direct causal link. NT5DC4, while less studied, may play a role in broader cellular functions, with its pseudogenization potentially impacting metabolic and immune health.

The researchers' work highlights a potential interaction between small population size, genetic drift, and reduced natural selection. In small populations, harmful mutations can persist due to the weakened ability of selection to remove them, which leads to amplified effects of genetic drift. In cheetahs, the prolonged low effective population size has exacerbated these issues, reducing their adaptive potential and intensifying the challenges of inbreeding depression.

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However, it should be stressed that the limited genomic data analyzed in the study, sourced from seven wild individuals and one captive individual, restricts broader insights at the population level. The functional impact of pseudogenes identified in the study requires further experimental validation to confirm their biological significance in fertility and immunity. For example, proteomic analyses could provide clarity on the extent of functional disruption caused by PTCs. Additionally, without a cheetah recombination map or more genomic data, the timeline of the emergence of these mutations remains uncertain. Current estimates suggest that they arose either after the cheetah-puma divergence, ~4.9 million years ago, or within the *A. jubatus* lineage, 32,000–67,000 years ago.

Advances in genomic technologies present new opportunities for monitoring and mitigating genetic erosion. For instance, CRISPR-based approaches for editing deleterious alleles are being explored in conservation genetics (Ansori et al., 2023), providing a potential avenue for addressing pseudogenization in cheetahs. These emerging tools, combined with habitat preservation and genetic rescue efforts, could help mitigate the challenges associated with genetic erosion and promote the long-term viability of bottlenecked species.

The study by Peers et al. (2025) underscores the importance of connecting genetic and ecological findings to broader patterns of pseudogenization, inbreeding depression, and conservation strategies. It becomes clear that addressing these genetic vulnerabilities will require a multifaceted approach. This could include not only genomics-informed interventions but also the preservation of ecological and evolutionary processes that sustain biodiversity.

Conflict of interest:

The author declares no conflict of interest.

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