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Breeding for Hypoallergenic Traits in Cats: Genetic Insights

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Abstract This study explores the genetic mechanisms behind hypoallergenic traits in cats, focusing on the role of Fel d 1, genetic variations linked to hypoallergenic traits, and current breeding methods, examines selective breeding practices, including the development of hypoallergenic breeds such as the Siberian cat, and explore emerging genomic technologies like CRISPR and genetic testing and also addresses ethical and environmental concerns associated with hypoallergenic cat breeding, including welfare considerations. The findings highlight significant progress in hypoallergenic cat breeding, while also emphasizing the need for continued research to overcome challenges in genetics and breeding practices. Future efforts should focus on refining breeding strategies and developing more efficient genomic tools, with the ultimate goal of offering hypoallergenic pets to a broader population of allergy sufferers.
Keywords Feline allergies; Hypoallergenic cats; Fel d 1; Genetic breeding; CRISPR gene editing

1 Introduction

Feline allergies are a significant health concern, affecting over 10% of the global population. These allergies are primarily triggered by the major cat allergen Fel d 1, which can lead to respiratory issues such as rhinitis and asthma (Luzar et al., 2016; Lee et al., 2023). The prevalence of cat allergies has been increasing, with a notable impact on individuals' quality of life, often resulting in the avoidance of cat ownership or the relinquishment of cats to shelters (Sparkes, 2021). The allergenic activity of cat allergens, particularly Fel d 1, is well-documented, with studies showing that it binds to specific IgE antibodies in sensitized individuals, leading to allergic reactions (Kaiser et al., 2003; Trifonova et al., 2023).

The development of hypoallergenic cats is crucial for allergy sufferers who wish to maintain a close relationship with their pets without experiencing adverse health effects. Hypoallergenic cats, such as those with reduced levels of Fel d 1, could significantly decrease allergic reactions in humans (Butt et al., 2012; Lee et al., 2023). Innovative approaches, including genetic modifications using CRISPR-Cas9 to create CH2 knockout cats with lower Fel d 1 levels, have shown promise in producing hypoallergenic cats. Additionally, immunization strategies that induce neutralizing antibodies against Fel d 1 in cats have been explored, potentially reducing allergen levels and alleviating symptoms in allergic individuals (Thoms et al., 2019; Thoms et al., 2020).

This study attempts to explore the current understanding of feline allergies, discuss the impact of these allergies on human health, provide an overview of potential solutions for allergy sufferers through the development of hypoallergenic cats, examine recent advancements in allergen-specific immunotherapy and genetic engineering, aiming to provide insights into effective strategies for managing cat allergies and improving the quality of life for those affected. Additionally, this study will discuss the implications of these developments for cat ownership and the human-cat bond, highlighting the importance of continued research in this field.

2 Genetic Basis of Allergic Reactions in Humans

2.1 The role of Fel d 1 in cat allergies

Fel d 1 is recognized as the primary allergen responsible for allergic reactions in humans to domestic cats. It is a low-molecular-weight protein that can cause severe allergic responses, including rhinitis, conjunctivitis, and asthma (Lee et al., 2023). The protein is composed of two heterodimers and has a structure similar to uteroglobin,

a molecule with anti-inflammatory properties. The allergenic properties of Fel d 1 are significant, as it is the most common cause of allergic asthma related to cats worldwide (Kaiser et al., 2003).

2.2 Genetic factors influencing human sensitivity to Fel d 1

Human sensitivity to Fel d 1 can vary, and genetic factors play a crucial role in this variability. The sequence of genes coding for Fel d 1, such as Ch1 and Ch2, can influence the allergenic properties of the protein. In Siberian cats, mutations in these genes have been identified, which may affect the synthesis of Fel d 1 and potentially reduce its allergenic properties. These genetic variations could serve as markers for breeding cats with lower allergenic potential (Sartore et al., 2017).

2.3 Other proteins involved in cat allergies

While Fel d 1 is the most significant allergen, other proteins may also contribute to cat allergies. The presence of multiple allergens in cat dander complicates the allergic response in humans. However, the focus remains on Fel d 1 due to its dominant role in triggering allergic reactions (Butt et al., 2012). The development of hypoallergenic cats, such as those with reduced Fel d 1 levels through genetic modifications, represents a promising approach to mitigating allergic reactions in sensitive individuals (Lee et al., 2023).

In summary, Fel d 1 is the primary allergen responsible for cat allergies, with genetic factors influencing its allergenic properties. Understanding these genetic influences can aid in breeding hypoallergenic cats, potentially reducing allergic reactions in humans.

3 Genetic Mechanisms Underlying Hypoallergenic Traits in Cats

3.1 Identification of hypoallergenic cat breeds

Hypoallergenic cat breeds are often identified based on their reduced production of the Fel d 1 protein, which is the primary allergen responsible for allergic reactions in humans. The Siberian cat is one such breed that is believed to have lower levels of this allergen. Genetic studies have shown that certain mutations in the genes responsible for Fel d 1 production may contribute to this reduced allergenic potential (Sartore et al., 2017). Additionally, the concept of hypoallergenic breeds has been commercialized, with companies marketing specific breeds as hypoallergenic, although scientific validation of these claims is limited (Butt et al., 2012).

3.2 Genetic variations related to hypoallergenic traits

Genetic variations that may contribute to hypoallergenic traits in cats include mutations in the *Ch1* and *Ch2* genes, which code for the Fel d 1 protein. In Siberian cats, specific mutations in these genes have been identified, which could potentially alter the allergenic properties of Fel d 1, thereby reducing its allergenic potential (Sartore et al., 2017; Anderson et al., 2021). These genetic variations are crucial for understanding how hypoallergenic traits can be selected and bred into cat populations.

3.3 Role of the Fel d 1 protein expression in hypoallergenic cats

The Fel d 1 protein is the major allergen in cats, and its expression levels are a key factor in determining the allergenic potential of a cat. Research indicates that certain breeds, like the Siberian cat, may have genetic mutations that lead to lower expression levels of Fel d 1, thus making them more suitable for individuals with allergies (Sartore et al., 2017). The identification of these genetic markers is essential for breeding programs aimed at producing hypoallergenic cats. However, the commercial claims of hypoallergenic breeds often lack comprehensive scientific backing, highlighting the need for further research in this area (Butt et al., 2012; Abitbol et al., 2024).

In summary, the identification of hypoallergenic cat breeds, understanding genetic variations related to hypoallergenic traits, and the role of Fel d 1 protein expression are critical components in breeding cats with reduced allergenic potential. These insights can guide future breeding programs and help in developing scientifically validated hypoallergenic cat breeds.

4 Current Breeding Approaches for Hypoallergenic Cats

4.1 Selective breeding for hypoallergenic traits

Selective breeding for hypoallergenic traits in cats primarily aims to reduce the production of allergenic proteins, particularly Fel d 1, which is the most common allergen responsible for allergic reactions in sensitive individuals. Fel d 1 is produced in the cat's saliva, sebaceous glands, and skin, and it spreads through grooming, making it a major source of allergens in the home environment. Breeders focus on selecting cats that naturally produce lower levels of Fel d 1, as well as other allergens like Fel d 2 and Fel d 4, which are found in the cat's skin and hair follicles. Advances in genetic testing have enabled breeders to identify specific genetic markers associated with reduced allergen production, facilitating more targeted and effective breeding strategies. By selecting breeding pairs that exhibit lower allergen levels, breeders can enhance these traits in subsequent generations, though achieving a truly hypoallergenic cat requires a delicate balance of genetics, environment, and care practices (Figure 1) (Thoms et al., 2019; Brackett et al., 2022; Lee et al., 2023).

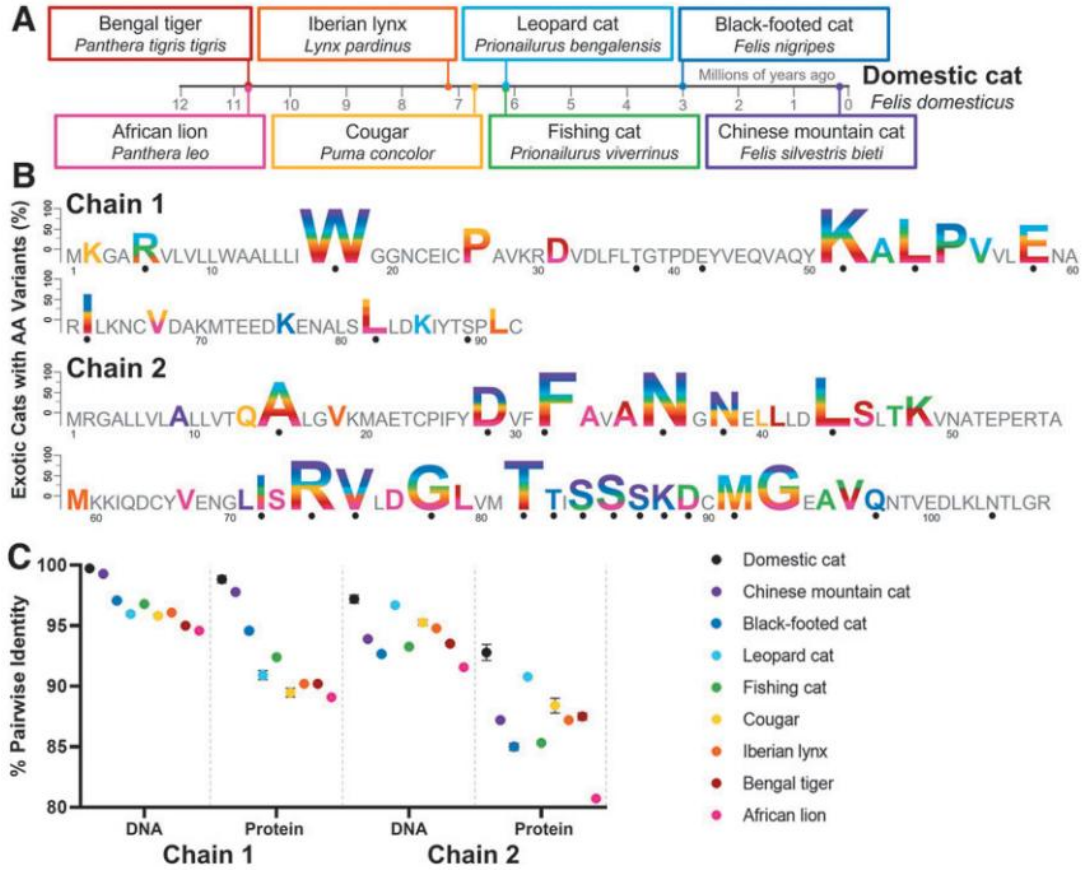

Figure 1 Comparative sequence analysis of exotic cat Fel d 1 orthologs (Adopted from Brackett et al., 2022)

Image caption: Fel d 1 orthologous sequences from 24 exotic cats, representing eight felid species, were analyzed. (A) Approximate evolutionary timeline of the domestic and exotic cats.38 (B) Amino acid sequences of Fel d 1 chains 1 and 2. The species (color) and percentage (font size) of exotic cats with sequence variants at a given amino acid residue were determined. Corresponding domestic cat variants are indicated; (C) Mean sequence identities of domestic and exotic cat species following pairwise alignments with the GenBank DNA or protein Fel d 1 references. Data represent the mean-standard error of the mean (SEM; 50 domestic cats, 3 cats per exotic species). Color-coded species legend (bottom right) corresponds to panels (A), (B), and (C) (Adopted from Brackett et al., 2022)

4.2 Case study: the development of the siberian cat as a hypoallergenic breed

The Siberian cat serves as a successful example of selective breeding for hypoallergenic traits. Native to Russia, the Siberian breed is known for producing significantly lower levels of Fel d 1 compared to many other cat breeds, making it an attractive option for allergic individuals. This breed's hypoallergenic characteristic is believed to be an innate trait, with several studies confirming that Siberian cats consistently show reduced allergen production. Selective breeding within the Siberian breed has focused on preserving this low allergen trait while maintaining

the breed's other desirable characteristics, such as its robust health, friendly personality, and striking appearance (Abitbol et al., 2024)). The development of the Siberian cat as a hypoallergenic breed was largely unintentional at first, but breeders have since recognized and enhanced this trait, making the Siberian one of the few breeds specifically known for its hypoallergenic potential. While not every Siberian cat will be hypoallergenic, the breed's overall lower production of Fel d 1 has established it as one of the most popular hypoallergenic breeds (Salonen et al., 2019).

4.3 Challenges and limitations in hypoallergenic cat breeding

Breeding for hypoallergenic traits in cats presents several challenges and limitations. One major difficulty is the genetic complexity of allergen production. The inheritance patterns of hypoallergenic traits are not fully understood, as the production of Fel d 1 and other allergens is influenced by multiple genes. This makes it difficult to predict the allergenic potential of offspring, even when breeding from hypoallergenic lines. Furthermore, variability in allergen levels within hypoallergenic breeds remains a significant challenge. Not all individuals within a breed like the Siberian cat will produce the same low levels of allergens, and some may still trigger allergic reactions (Brackett et al., 2022). Additionally, selective breeding focused solely on hypoallergenic traits can lead to ethical concerns about inbreeding and its potential consequences, such as a reduced gene pool and the increased risk of genetic disorders. While hypoallergenic breeding aims to produce cats with fewer allergens, it is important to balance this goal with the long-term health and genetic diversity of the breed. Moreover, environmental factors, such as diet, grooming, and general health, can influence allergen production, further complicating the breeding process. Despite these efforts, achieving a completely hypoallergenic cat remains elusive, as even hypoallergenic breeds can produce sufficient allergens to trigger reactions in some sensitive individuals (Thoms et al., 2020; Bienboire-Frosini et al., 2020).

5 Genomic Technologies in Hypoallergenic Cat Breeding

5.1 Use of genetic testing in identifying hypoallergenic traits

Genetic testing plays a crucial role in identifying hypoallergenic traits in cats by analyzing the distribution and frequency of genetic variants associated with allergens. For instance, extensive panel testing has been used to identify disease-associated variants across various cat breeds, which can be instrumental in reducing allergen levels through selective breeding. The use of high-throughput SNP genotyping technologies, such as the feline 63K DNA array, has improved the genetic dissection of traits, allowing breeders to identify and select for hypoallergenic traits more efficiently. These technologies enable breeders to assess genetic diversity and identify specific markers associated with hypoallergenic traits, thereby supporting breeding programs aimed at reducing allergens like Fel d 1 (Figure 2) (Gandolfi et al., 2018; Anderson et al., 2021).

Figure 2 A)The signature "smile" of a cat with Myotonia Congenita; B) The rare coat color phenotype Amber in a random-bred cat from Finland; C) Polydactyly variant Hw also associated with extra toes in all four feet. Photo credit (from A to C): Kimberly Sullivan, Ari Kankainen, Samantha Bradley (Adopted from Anderson et al., 2021)

5.2 CRISPR and gene-editing technologies for hypoallergenic traits

CRISPR-Cas9 technology has emerged as a powerful tool for creating hypoallergenic cats by enabling precise gene editing. Recent studies have demonstrated the successful use of CRISPR to knock out the CH2 gene in cats, resulting in significantly reduced levels of the major allergen Fel d 1 (Lee et al., 2023). This gene-editing approach offers a promising avenue for developing hypoallergenic cats by directly targeting and modifying the

genes responsible for allergen production. The ability to edit specific genes with high precision makes CRISPR a transformative technology in the field of hypoallergenic cat breeding, providing a method to potentially eliminate allergens at their genetic source (Brackett et al., 2022; Wang and Doudna, 2023).

5.3 Future possibilities of genomic approaches

The future of genomic approaches in hypoallergenic cat breeding is promising, with potential advancements in both genetic testing and gene-editing technologies. As genomic databases grow and integrate more comprehensive phenotype information, the accuracy of predicting hypoallergenic traits will improve, facilitating more effective breeding strategies (Vanraden et al., 2020; Weckwerth et al., 2020). Additionally, the continued development of CRISPR and other gene-editing technologies will likely lead to more refined and efficient methods for reducing allergens in cats, potentially expanding to other allergenic proteins beyond Fel d 1 (Wang and Doudna, 2023). These advancements could revolutionize the breeding of hypoallergenic cats, making it possible to tailor genetic modifications to meet specific allergenic profiles and improve the health and welfare of both cats and their owners.

In summary, the integration of genetic testing and CRISPR technologies holds significant potential for advancing hypoallergenic cat breeding. These genomic technologies enable precise identification and modification of allergenic traits, paving the way for the development of cats that are more suitable for allergy sufferers.

6 Ethical and Environmental Considerations

6.1 Ethical concerns in breeding for hypoallergenic traits

One of the most pressing ethical concerns in breeding hypoallergenic cats is the risk of inbreeding. Selective breeding for specific traits, such as hypoallergenic characteristics, often involves a limited gene pool, which can lead to the exacerbation of genetic disorders and health issues in the cats being bred. This reduction in genetic diversity can result in higher rates of congenital defects, reduced fertility, and other health problems, which may compromise the welfare of the animals (Hu and Zhao, 2023; Menor-Campos et al., 2024). Additionally, focusing solely on hypoallergenic traits may overlook other essential aspects of a cat's well-being, such as temperament, socialization, and physical health. Ethical breeding should prioritize not only allergen reduction but also the long-term health and genetic vitality of the breed to prevent the emergence of undesirable traits that could harm the animals in future generations (Holst, 2022).

6.2 Environmental impact of breeding hypoallergenic cats

The environmental impact of breeding hypoallergenic cats is another important consideration. While the ecological footprint of cat breeding itself may not be as large as that of industrial farming, it still requires the use of resources such as food, veterinary care, and housing. Additionally, the demand for hypoallergenic cats can lead to overproduction or unsustainable breeding practices if breeders attempt to meet high consumer demand without regard for genetic health or environmental sustainability (Liem et al., 2019; Da Silva et al., 2024). Breeding programs that prioritize hypoallergenic traits could also unintentionally encourage the commercialization of certain breeds at the expense of others, potentially contributing to the endangerment of less popular breeds and reducing overall biodiversity. Moreover, the environmental impact of excessive demand for pets in general can lead to issues such as overpopulation and the strain on animal shelters, which may be left with cats that are difficult to rehome or adopt due to the growing preference for hypoallergenic breeds (Lee et al., 2023).

6.3 Considerations for animal welfare

Animal welfare is a central concern in the breeding of hypoallergenic cats, as the emphasis on specific traits must not come at the expense of the animals' overall health and well-being. Cats bred for hypoallergenic traits must still receive adequate care, socialization, and enrichment to ensure they are physically and mentally healthy. Breeding for specific traits such as reduced allergen production can sometimes lead to unintended side effects, including poor coat condition, respiratory problems, or other hereditary conditions that compromise quality of life. Furthermore, breeders must ensure that the cats they produce are placed in responsible homes that are prepared to meet their care needs, avoiding situations where animals are neglected or abandoned (Hilger et al., 2024). Ethical breeding programs should focus on the well-being of the cats, ensuring they are bred not only for hypoallergenic

traits but also for strong immune systems, good temperaments, and the ability to live fulfilling lives. Additionally, breeders should follow guidelines set forth by veterinary professionals to reduce the risk of health complications and ensure the overall welfare of the animals they produce (Boeykens et al., 2024).

7 Concluding Remarks

The breeding of hypoallergenic cats has made significant strides in recent years, with selective breeding programs focusing on reducing the production of allergenic proteins, particularly Fel d 1, which is the primary culprit for allergic reactions in sensitive individuals. Key findings indicate that certain cat breeds, such as the Siberian and Balinese, naturally produce lower levels of Fel d 1, making them more suitable for people with cat allergies. Advances in genetic testing have allowed breeders to identify specific genetic markers associated with hypoallergenic traits, enabling more targeted and efficient breeding strategies. However, variability in allergen production within hypoallergenic breeds and the complex genetics of allergen expression present challenges in guaranteeing consistent hypoallergenic traits in all individuals. Despite these advancements, achieving a completely hypoallergenic cat remains an elusive goal, as no breed has been found to produce zero allergens. The study highlights the balance required between breeding for hypoallergenic traits and maintaining the overall health, welfare, and genetic diversity of cat populations.

Future research in hypoallergenic cat breeding should focus on unraveling the genetic basis of allergen production in more detail. While the role of Fel d 1 is well-established, the involvement of other allergens, such as Fel d 2 and Fel d 4, remains less understood, and their contribution to allergic reactions warrants further exploration. Advances in genomics and gene editing technologies, such as CRISPR, could offer promising avenues for directly modifying the genes responsible for allergen production, potentially leading to more effective hypoallergenic cats. Additionally, research should aim to identify genetic markers that predict reduced allergen levels, allowing breeders to select for hypoallergenic traits more accurately. Further studies into the environmental factors influencing allergen production, such as diet, grooming practices, and overall health, could also improve the predictability of hypoallergenic traits across different environments. Understanding how hypoallergenic traits are inherited will be essential for creating sustainable breeding programs that maintain genetic diversity while enhancing hypoallergenic characteristics.

The development of hypoallergenic cats holds significant implications for both pet owners and the allergy community. For individuals with cat allergies, hypoallergenic breeds offer a potential solution to living with feline companions without triggering severe allergic reactions. However, it is important for pet owners to understand that no cat breed is entirely hypoallergenic, and even hypoallergenic cats can still produce sufficient allergens to cause reactions in some individuals. Pet owners must consider not only the breed but also the specific cat's allergen levels, and take steps such as regular grooming, environmental control, and air purification to reduce allergens in the home. For the allergy community, these developments provide a promising alternative to conventional allergy treatments, such as medications and immunotherapy. However, further education on the limitations of hypoallergenic cats is essential to set realistic expectations. As research continues and breeding programs evolve, hypoallergenic cats may become more widely available, offering a new opportunity for allergic individuals to experience the companionship of a cat without the burden of allergic reactions.

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Conflict of Interest Disclosure

Author affirms 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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