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Perspective

Feline Radial Hemimelia and Cardiac Anomalies: A Comprehensive Understanding

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INTRODUCTION

Feline Radial Hemimelia (RH) stands as a congenital skeletal disorder that significantly disrupts the typical development of forelimbs in cats, particularly impacting the radius and ulna. This disorder, while relatively rare, can present with varying degrees of severity, profoundly influencing the mobility and overall quality of life for affected feline individuals. In this endeavor to understand the intricacies of RH, we embarked on an in-depth study focusing on Siamese cats, a breed notably susceptible to this condition. The investigation involved an extensive Siamese cat pedigree, encompassing 18 individuals, aiming to unravel the genetic underpinnings of RH and intriguingly, its potential cardiac implications [1].

DESCRIPTION

The pedigree analysis yielded crucial insights into the mode of inheritance, revealing an autosomal recessive pattern for RH. The presence of affected kittens from an unaffected queen and her backcrossed unaffected sire underscored the genetic basis of RH, aligning with previous observations in both Siamese and domestic shorthair cats [2]. Understanding this inheritance pattern holds immense significance, as it paves the way for effective breeding strategies to curtail the spread of RH within feline populations.

Radiographic assessments emerged as a pivotal tool in comprehending the severity and classification of RH. These assessments showcased varying degrees of dysplasia in affected kittens, particularly concerning the radius, ulna and humerus. Moreover, the identification of extra ribs and kinked tails in affected kittens added an intriguing layer of complexity to the genetic underpinnings of RH. Although these associated anomalies were not directly linked to specific genetic variants in our study, they certainly warrant further exploration into potential interactions and overlapping genetic pathways. The subsequent whole-genome sequencing and variant analysis highlighted candidate genes, notably *CMYA5* and *JMY*, as potential contributors to RH. These genes have established associations with bone development and cardiac function in humans, rendering them plausible candidates for the observed skeletal abnormalities and potential cardiac implications in affected Siamese cats. The identified variants, especially those in *CMYA5*, exhibited loss-of-function effects, further emphasizing their potential pathogenicity.

Interestingly, our study delved into the potential cardiac implications associated with RH. Echocardiography in affected kittens unveiled signs of congenital cardiac abnormalities, notably a large left atrium. While cardiac manifestations were not the primary focus of this study, these findings provide valuable insights into potential secondary effects of RH on cardiac health. Future research investigating the cardiac aspect of RH may unravel the intricate interplay between genetic variants and cardiac anomalies, offering a more comprehensive understanding of this condition.

The genetic underpinnings of RH are undoubtedly heterogeneous and major causative genes, such as *SALL4* or *TBX5*, have been identified. In the context of our study, the causative mutation found in the *CMYA5* gene suggests that *CMYA5* may be a transcription factor essential for proper forelimb formation, akin to the roles of *SALL4* and *TBX5* in heart development. Despite being an under-studied striated muscle protein, *CMYA5* has garnered significant attention in various scientific studies, associating it with cardiac dyad architecture, tibial and limb-girdle muscle dystrophies, schizophrenia and different types of cancer [3-7]. The recent revelation of *CMYA5* as a novel interaction partner of FHL2 in cardiac myocytes further corroborates its potential role in cardiac health [8]. The juxtaposition of *CMYA5* to Z-lines during cardiac development accentuates its relevance, preceding junctional sarcoplasmic reticulum positioning or transverse tubule formation. Moreover, TBX5's crucial role in cardiac conduction system patterning and mature cardiomyocyte function further emphasizes the significance of genes like *CMYA5* in heart development [9].

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CONCLUSION

In conclusion, this comprehensive study delving into the genetic basis and potential cardiac implications of RH in Siamese cats shed significant light on its autosomal recessive mode of inheritance and the varying degrees of dysplasia that underscore the complexity of RH. The identification of candidate genes, *CMYA5* and *JMY*, has opened doors for further research into their roles in bone development and cardiac function, offering exciting prospects for potential therapeutic interventions. Understanding these intricate genetic mechanisms is crucial not only for the development of targeted diagnostics but also for informing responsible breeding practices, ensuring the well-being of Siamese cats, and potentially contributing to advancements in human medicine.

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