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Candidate Gene Discovery for Retained Testicles in Dogs

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Summary and Implications

Cryptorchidism, or retained testicles, is one of the most common congenital developmental defects in purebred dogs. DNA markers called single nucleotide polymorphisms (SNPs) are being used to investigate the associations between 21 candidate genes and cryptorchidism in Siberian huskies. We found the genes *COL2A1*, *HOXA10*, *INSL3* and *TIMP1* tended to be associated with cryptorchidism in Siberian huskies. The results will help to find the causative mutations in the future and will be useful in dog breeding programs to reduce the incidence of cryptorchidism.

Introduction

Having a dog with one or both testicles retained (cryptorchidism) is one of the most common congenital developmental defects in purebred dogs. Cryptorchidism is heritable and is a sex-limited autosomal recessive trait in dogs. The incidences of cryptorchidism in dogs range from 1.2 to 10%. In several dog breeds, it is as high as 15 percent. Dogs with cryptorchidism may have reduced fertility or be infertile at adulthood. If retained testicles are kept intact in the dog, there is a significant risk of testicular cancer. In order to predict the risk of this abnormality in a male dog or the progeny or parents, candidate gene analysis and comparative gene mapping studies will be conducted to search for genes associated with cryptorchidism in Siberian huskies. The ultimate goal of this research is to develop a genetic test for breeders to use to remove male carriers of this abnormality from the breeding population.

Materials and Methods

Dog cheek (buccal) swabs have been collected by dog owners from 65 Siberian husky families including parents, affected offspring and non affected male sibs. DNA samples were extracted from buccal swabs of 167 Siberian Huskies in total.

Candidate genes were selected due to their biological functions and comparative mapping information from other species. DNA markers-- SNPs were discovered using the following steps. First, we sequenced parts of each gene and then examined DNA pools from dogs with or without cryptorchidism selected from several families. Further, direct sequencing to discover possible SNPs was then used. Thirdly, these SNPs were genotyped in full sibling dogs and statistical association analyses were performed. If there

were satisfactory results, then interesting DNA markers were genotyped in the remaining dog samples and more statistical analyses were conducted based on the whole genotyping results.

Results

To date, 74 DNA markers have been found in the 21 candidate genes chosen. By using direct sequencing or restriction enzyme digestion, 44 SNPs have been genotyped in the 16 pairs of full-sibs (no more full-sibling pairs could be found in the current dogs sampled). Six important SNPs were found that appeared to be associated with cryptorchidism from the full-siblings statistical analyses and have been genotyped further in all dogs. More SNPs are still being discovered, and need to be genotyped completely in the remaining dog samples. Statistical analyses have been completed with our current SNP data. Four genes including *COL2A1*, *HOXA10*, *INSL3* and *TIMP1* showed likely associations with cryptorchidism in Siberian Huskies.

Discussion

Since several potentially associated genes have been found in this study, adding more dog samples will increase the power to detect the associated DNA markers. It is possible that different genes might be responsible for cryptorchidism in different dog breeds, of even within different families in the same breed. When more dog samples are collected, additional association analyses will be performed based on different clinic classifications such as unilateral or bilateral cryptorchidism. It will increase the detecting power for associated DNA marker as well. When informative SNPs and linkage to cryptorchidism are found, causative mutation screening will be examined further. The identified gene(s) in our families could be used in further investigations to analyze the role(s) of suspected genes in different dog breeds. Our possible finding of causative mutations in the future for canine cryptorchidism could be immediately applied by dog breeders in their breeding program to reduce the incidence of cryptorchidism.

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