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Candidate Gene Discovery for Dog Cryptorchidism

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Summary and Implications
Cryptorchidism is one of the most common developmental defects in purebred dogs. Single gene markers (called SNPs) are being used to investigate the associations in Siberian huskies between candidate genes (INSL3, LGR8, ESR1, HOXA10, MIS, CGRP and other positional candidates) and cryptorchidism. Findings of causative mutations in candidate genes will be useful in dog breeding programs to reduce the incidence of cryptorchidism.

Introduction
Cryptorchidism, or a retained testicle, is a condition in males wherein the testis does not successfully descend from its intra-abdominal location into the scrotum. The name “cryptorchidism” containing the term “orchid” comes from medieval European herbalists’ belief that bulbs of common European orchids looked like testicles [Figure 1]. The frequency of cryptorchidism in several dog breeds is as high as 15 percent. Dogs with cryptorchidism may have reduced fertility or infertility at adulthood. If a dog with a retained testicle is kept intact, 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 [Figure 2]. The ultimate goal of this research is to develop a genetic test to remove carriers of this abnormality.

Materials and Methods
Samples of DNA are being collected from 40 affected Siberian husky families including parents, affected offspring and non-affected male sibs.

Single nucleotide polymorphisms (SNPs) will be discovered first from the INSL3, LGR8, ESR1, MIS, CGRP and HOXA10 genes which are implicated in the development of cryptorchidism. First, we will sequence parts of each gene and then examine DNA pools from dogs with or without cryptorchidism selected from several families. Further, direct sequencing to discover possible SNPs will then take place. Thirdly, these SNPs will be genotyped in all families and statistical association analyses will be performed.

If no satisfactory results come from the above mentioned candidate genes, data from other positional candidate genes from comparative mapping in other species, especially our ongoing work in pigs can also be examined in the Siberian husky pedigrees.

Discussion
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. It is possible that different genes might be responsible for cryptorchidism in different dog breeds. As a result, the SNPs in other candidate genes can also be used for genetic examination of their potential roles in cryptorchidism in these breeds. Our possible finding of causative mutations for canine cryptorchidism can be immediately applied by dog breeders in their breeding program to reduce the incidence of cryptorchidism.

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