Bayesian Inference Identifies a Candidate Region Associated with Canine Cryptorchidism that Includes the *AMHR2* Gene

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Summary

Cryptorchidism, or retained testicles, is one of the most common congenital developmental defects in purebred dogs. A genome wide association study (GWAS) was performed using the CanineHD BeadChip. Genotyping data was analyzed by case-control analysis in PLINK software and the BayesB approach in GenSel software with the genome partitioned into 1Mb windows of SNPs or haplotypes. No significant association was observed in the case-control analyses after corrections for False Discovery Rate (FDR) in PLINK. In contrast, the BayesB analysis identified a 1Mb region on dog chromosome 27 (CFA27) containing the *AMHR2* (anti-mullerian hormone type II receptor) gene that explained a high percentage of genetic variance. In conclusion, we identified a putative candidate region at the 4th Mb on CFA27 (CanFam2.0) harboring a very promising functional candidate gene *AMHR2* associated with the development of cryptorchidism in our Siberian Husky population.

Introduction

Having a dog with one or both testicles retained is one of the most common congenital developmental defects in purebred dogs. The incidence of cryptorchidism in dogs ranges from 1.2 to 14%. An undescended testicle is considered a risk factor for germ-cell tumors and bilateral cryptorchidism can result in male infertility. Cryptorchidism is heritable and is a sex-limited trait. Here we performed a genome wide association study in Siberian Husky dogs to identify genomic regions and propose some positional candidate genes associated with variation in the incidence of cryptorchids.

Materials and Methods

A total of 205 male Siberian Husky samples were collected from USA, the UK and Canada in this study. There were 106 dogs with cryptorchidism and 99 diagnosed as normal. DNA samples were extracted from buccal swabs or obtained directly from Canine Health Information Center (CHIC) DNA repository. DNA samples were sent to GeneSeek, Inc. (Lincoln, NE, USA) for genotyping on the CanineHD BeadChip. STRUCTURE software was used for inferring population structure and grouping like dogs. Genome wide association studies were carried out separately on each of the subgroups. Three approaches were applied for the data analyses including 1) case-control analysis in PLINK using single SNP markers; 2) BayesB model averaging approaches in GenSel to obtain the variance explained by SNPs in one megabase (1Mb) genomic windows (SNP model) and 3) explained by haplotypes in 1Mb windows (haplo type model).

Results

Here we re-assigned Siberian Huskies into 3 subgroups according to Q values in STRUCTURE. No significant association was observed in the case-control analyses after FDR corrections in PLINK for any subgroup or the combined population. In contrast, for subgroup 1, three 1Mb windows on CFA27, and one window on CFA1 and CFA14 were detected using BayesB analyses with either the SNP or haplotype models. A candidate gene named anti-mullerian hormone type II receptor (*AMHR2*) is located in the region detected in subgroup 1, namely the 4th Mb of CFA27. Moreover, one window at the 75th Mb on CFA4 for subgroup 2 and at the 18th Mb on CFA31 for subgroup 3 were detected by both SNP and haplotype models. No apparent candidate genes in these regions have so far been reported to be associated with the processes of testicular descent or the development of cryptorchidism.

Discussion

The dog subgroups were consistent for the most part with their geographic distribution but the regions identified in each subgroup were distinctly different in each subgroup. This demonstrates that different genes might contribute to cryptorchidism in different groups of dogs. It is known that anti-mullerian hormone (AMH) mediates male sex differentiation by regression of mullerian ducts that would otherwise differentiate into the uterus and fallopian tubes. Mutations in *AMH* and *AMHR2* have been found to cause persistent mullerian duct syndrome (PMDS), and 60-70% patients with PMDS showed their testes located in the abdomen without descending into scrotum. Gene disruptions of *AMHR2* could prompt the development of undescended testicles in males. In conclusion, the important finding in this present GWAS is that the *AMHR2* gene was identified in a putative candidate region associated with canine cryptorchidism by using 1Mb window approach and Bayesian inference.

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