Common variants in the *CPT1A* gene are associated with cataract in Northern breeds of domestic dog

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Background and Aims

Primary hereditary cataract affects a significant number of purebred domestic dog breeds and is a major cause of blindness in dogs. Cataracts are common in Northern breeds such as the Siberian Husky, Alaskan Malamute and Samoyed, but their aetiology is currently unknown. To date there are only two genetic loci reported to be causally related to primary hereditary cataract in the dog.

To search for genetic loci associated with cataracts in Northern breeds, we used a genome-wide association study approach in three breeds—Siberian Husky, Alaskan Malamute and Samoyed. Cases were defined as dogs with bilateral posterior polar subcapsular cataracts and controls were at least four years of age with no evidence of cataracts or other ocular abnormality.

Genome-wide association study

The genome-wide association study (GWAS) of hereditary cataract (HC) in the Siberian Husky included 33 cases and 61 controls and 105,918 SNPs. This identified a region on canine chromosome 18 showing strong statistical association with HC ($P=1.1 \times 10^{-7}$) that exceeded Bonferroni significance ($P=4.7 \times 10^{-7}$) (**Figure 1**).

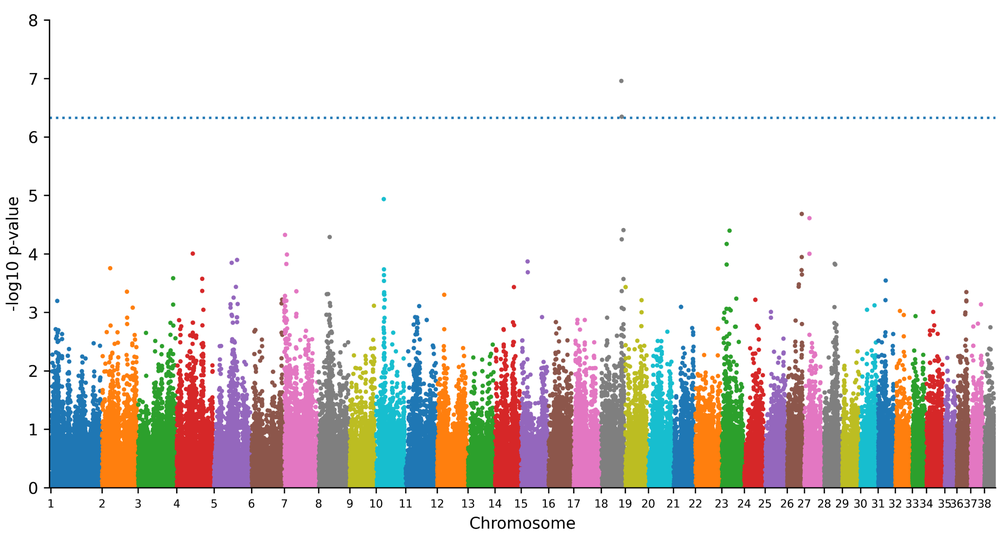

Figure 1. GWAS of HC in the Siberian Husky. The horizontal blue dotted line denotes Bonferroni significance.

We did not find any associations reaching Bonferroni significance in the Alaskan Malamute or Samoyed GWAS, although the Samoyed showed a suggestive signal in the same broad genomic region ($P=2.4 \times 10^{-5}$) (**Figure 2**).

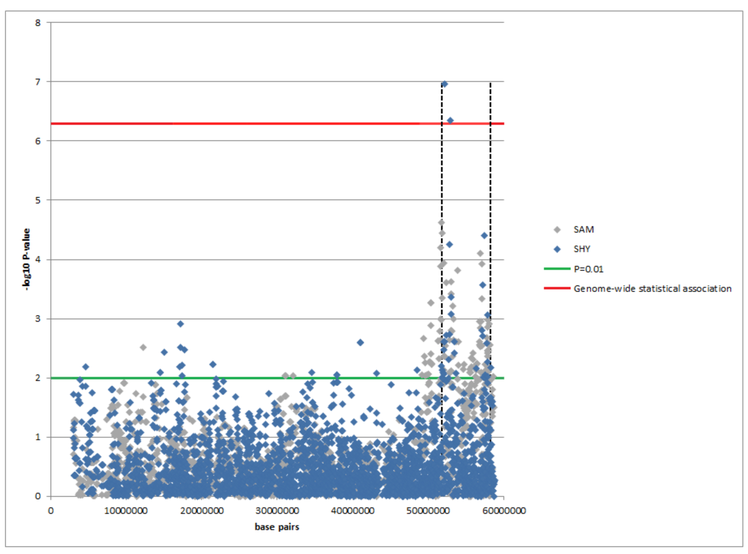

Figure 2. GWAS of HC in the Siberian Husky. Regional association plot of genomic region surrounding HC signal on CFA18 in Siberian Husky (SHY) and Samoyed (SAM). The horizontal red line denotes Bonferroni significance and the green line represents the empirical statistical threshold used to delineate the critical region in the Siberian Husky (P-value <0.01).

Replication study

We obtained sequence data for the 6.5 Mb critical region using target capture in ten Huskies (five cases and five controls). Analyses of these data and replication in additional sample sets and breeds revealed an exonic SNP within the *CPT1A* gene that showed statistical association with HC in four Northern breeds of dog (**Table 1**). However, this variant is common in the breed and on its own is not predictive of HC status (it is common in unaffected dogs) and there are some inconsistencies in other breeds; namely the Alaskan Malamute where the variant appears very common in the breed; and Lapponian Herder where the association appears reciprocal, albeit weak, so could be due to chance (**Table 1**).

Table 1. Association between exonic *CPT1A* SNP and HC in Northern breeds.

				Allele freq. (cases/controls)		
Breed	Case definition ‡	Control definition ∞	n cases/controls	Risk allele	Non-risk allele	Fisher's exact P-value
Siberian Husky	OU PPSC	NAD	43 / 138	0.98 / 0.66	0.02 / 0.34	6.3×10^{-11}
Samoyed	OU PPSC	NAD >=6 years of age	30 / 83	0.68 / 0.34	0.32 / 0.66	1.3×10^{-5}
Alaskan Malamute	OU PPSC	NAD	46 / 120	0.91 / 0.88	0.09 / 0.13	0.83
Icelandic Sheepdog	OU PPSC	NAD >=6 years of age	12/35	1.00 / 0.50	0.00 / 0.50	3.0×10^{-5}
Norwegian Buhund	OU PPSC	NAD	10/9	1.00 / 0.61	0.00 / 0.39	0.01
Finnish Lapphund	OU PPSC	NAD >=6 years of age	27 / 81	0.65 / 0.61	0.35 / 0.38	0.32
Lapponian Herder	OU PPSC	NAD >=6 years of age	15 / 68	0.73 / 0.85	0.27 / 0.15	0.03

‡ OU PPSC: bilateral posterior polar subcapsular cataract

∞ NAD: no abnormality detected

We are currently conducting analyses of whole genome sequence data from a Siberian Husky, Samoyed, Norwegian Buhund and Alaskan Malamute to supplement this dataset and to search for additional variants that may underlie this association.

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