TOWARDS A DEEPER UNDERSTANDING OF THE GENETICS UNDERLYING CANINE HYPOTHYROIDISM: TWO STUDIES IN DIFFERENT DOG BREEDS

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HYPOTHYROIDISM

One of the most common endocrine diseases in dogs. Susceptibility varies in different breeds. Major role of genetic risk factors in the development of this complex disorder

Four high-risk breeds included in two studies (study I and study II)

Gordon Setter (GO)
Hovawart (HV)
Rhodesian Ridgeback (RR)
Giant Schnauzer (GS)

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STUDY I

A Multi-Breed Genome-Wide Association Analysis for Canine Hypothyroidism Identifies a Shared Major Risk Locus on CFA12.

Bianchi M[1], Dahlgren S[2], Massey J[3], Dietschi E[4], Kierczak M[1], Lund-Ziener M[2], Sundberg K[5], Thoresen SI[2], Kämpe O[6], Andersson G[5], Ollier WE[3], Hedhammar Å[7], Leeb T[4], Lindblad-Toh K[8], Kennedy LJ[3], Lingaas F[2], Rosengren Pielberg G[1].

Three breeds: GO n=165, HV n=74, RR n=92

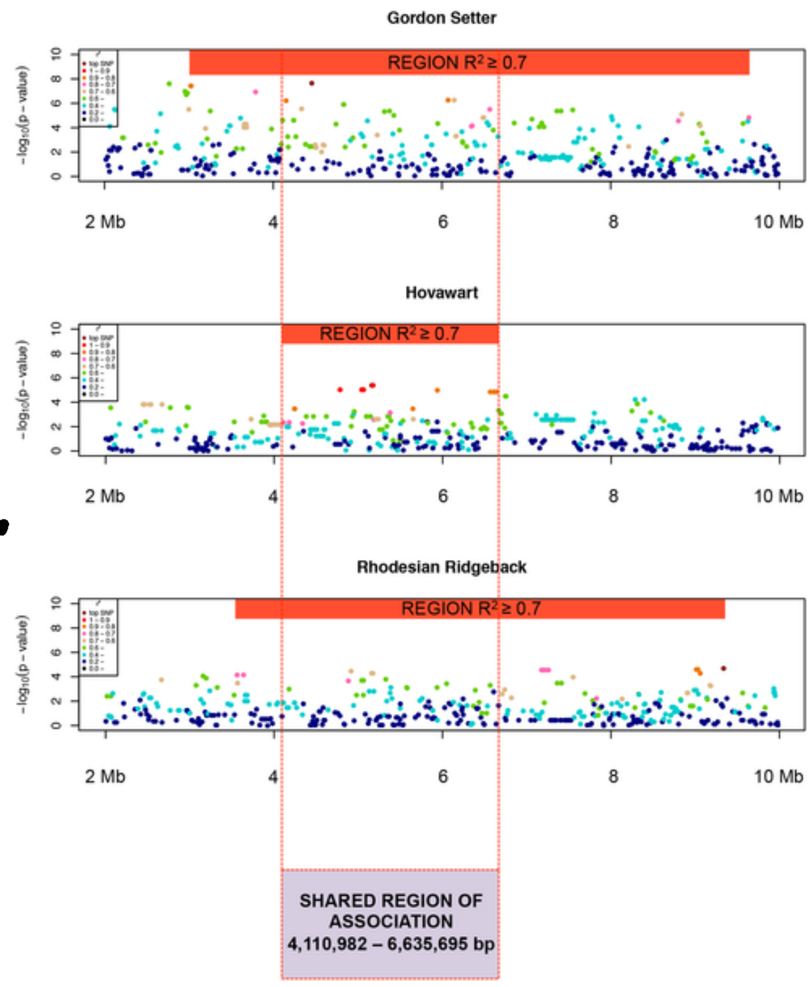
CASES: clinical diagnosis supported by TSH (> 40 mU/l) and fT4 (< 7 pmol/l).

CONTROLS: clinically healthy, dogs older than seven years of age

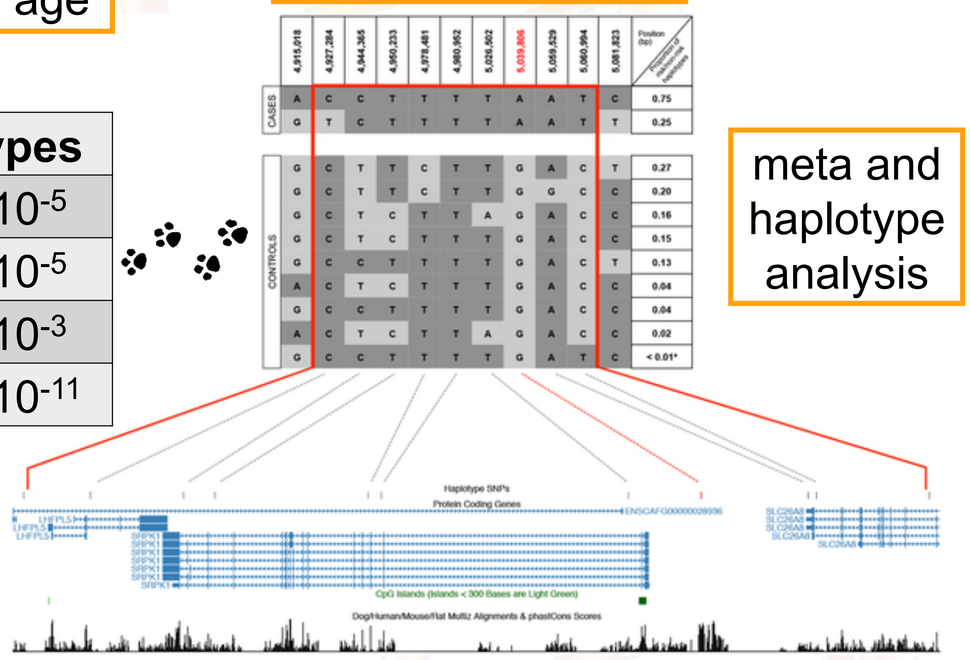
Samples genotyping using 170k SNP markers, followed by individual and marker-based quality control

breed-specific association analysis

Breed-specific and shared region of association on CFA12



Breed	Haplotype	Genotypes
GS	$p = 7.3x10^{-4}$	$p < 3.4x10^{-5}$
HV	$p = 5.3x10^{-5}$	$p = 1.0x10^{-5}$
RR	$p = 8x10^{-4}$	$p = 3.0x10^{-3}$
ALL	$p = 4.5x10^{-11}$	$p < 3.1x10^{-11}$



meta and haplotype analysis

The defined shared risk haplotype is enriched in cases from all the three breeds

The shared risk haplotype harbours three genes (*LHFPL5*, *SRPK1* and *SLC26A8)* that are novel with respect to their involvement in hypothyroidism

STUDY II

We have measurements for thyroglobulin auto-antibodies (TgAA), specific of autoimmune thyroiditis.

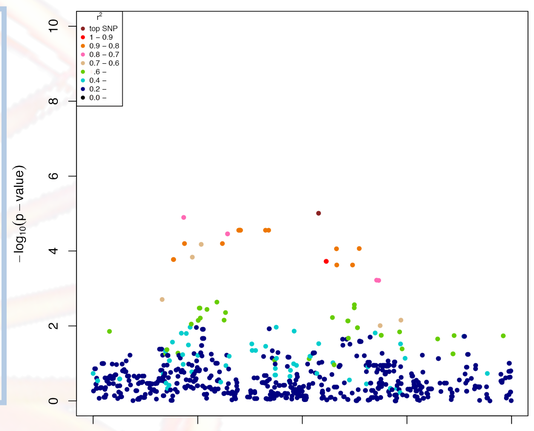
One breed: GS n=115

CASES: TSH (> 40 mU/L) and/or positive TgAA

CONTROLS: dogs older than seven years of age, negative TgAA, TSH ≤ 25 mU/l, fT4 ≥ 5pmol/l

Samples genotyping using 170k SNP markers, followed by individual and marker-based quality control.

Association analysis revealed a long (9 Mb) protective haplotype (no CFA12)

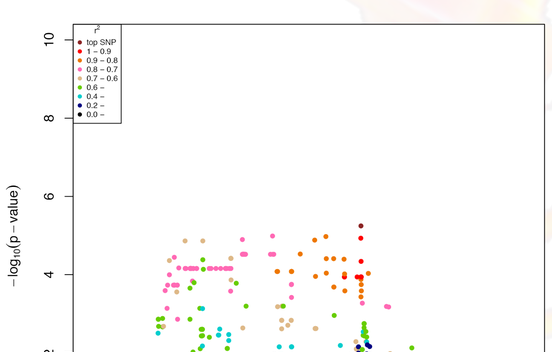


Sequencing of individuals representing protective and non-protective haplotype and SNPs detection

Selection of SNPs and genotyping in all samples

Missing SNPs inference and new association analysis

Shortening of the associated locus to a ~4Mb region



The locus harbours a gene linked to human thyroiditis development and to immune response. A preliminary analysis suggests a potential structural variant affecting the function of this candidate gene

OVERALL CONCLUSIONS

- increased knowledge about hypothyroidism etiology
- potential contribution to improved screening, breeding and disease treatment
- possible help for both dogs and humans