DOG GENETIC BACKGROUND EFFECT IS PREDOMINANT ON CLINICAL-IMMUNOLOGICAL TRAITS OF THE CANINE VISCERAL LEISHMANIASIS

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INTRODUCTION

The domestic dog (*Canis lupus familiaris*) is the main reservoir of the visceral leishmaniasis (VL) in urban environment and a model for study of VL. Explore the genetic basis of the *Leishmania infantum* natural infection in domestic dogs can increase the understanding of the balance of different factors that lead to different clinical-immunological outcomes in visceral leishmaniasis.

AIM

To investigate how much impact the dog genetic background (DGB) has on canine VL (CVL).

METHODS

Set of 234 dogs from Brazil: genomic DNA from blood samples was genotyped by SNPchip Canine HD (Illumina) with 118,786 SNPs

CVL traits: clinical outcome, parasite load, humoral immunity, cell-mediated immunity, and oxidative stress
Epidemiological covariates: geographic origin, age, sex, repellet collar, CVL vaccine, CVL treatment

Assessment of the traits and residual of traits + epidemiological covariates distributions

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Prior Heritability Analysis: evaluation of the distribution of trait + covariate + kinship matrix residues

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Selection of the best model based on qqplots, prior heritability analysis and distribution of residues

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Residual normalization (selected model): outlier removal, logarithmic transformation, box-cox transformation

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REML heritability analysis (HA) and association test between genotypes and phenotypes (Single SNP - GWAS) on LDAK Software

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Cutoff: 5% percentile of permutation

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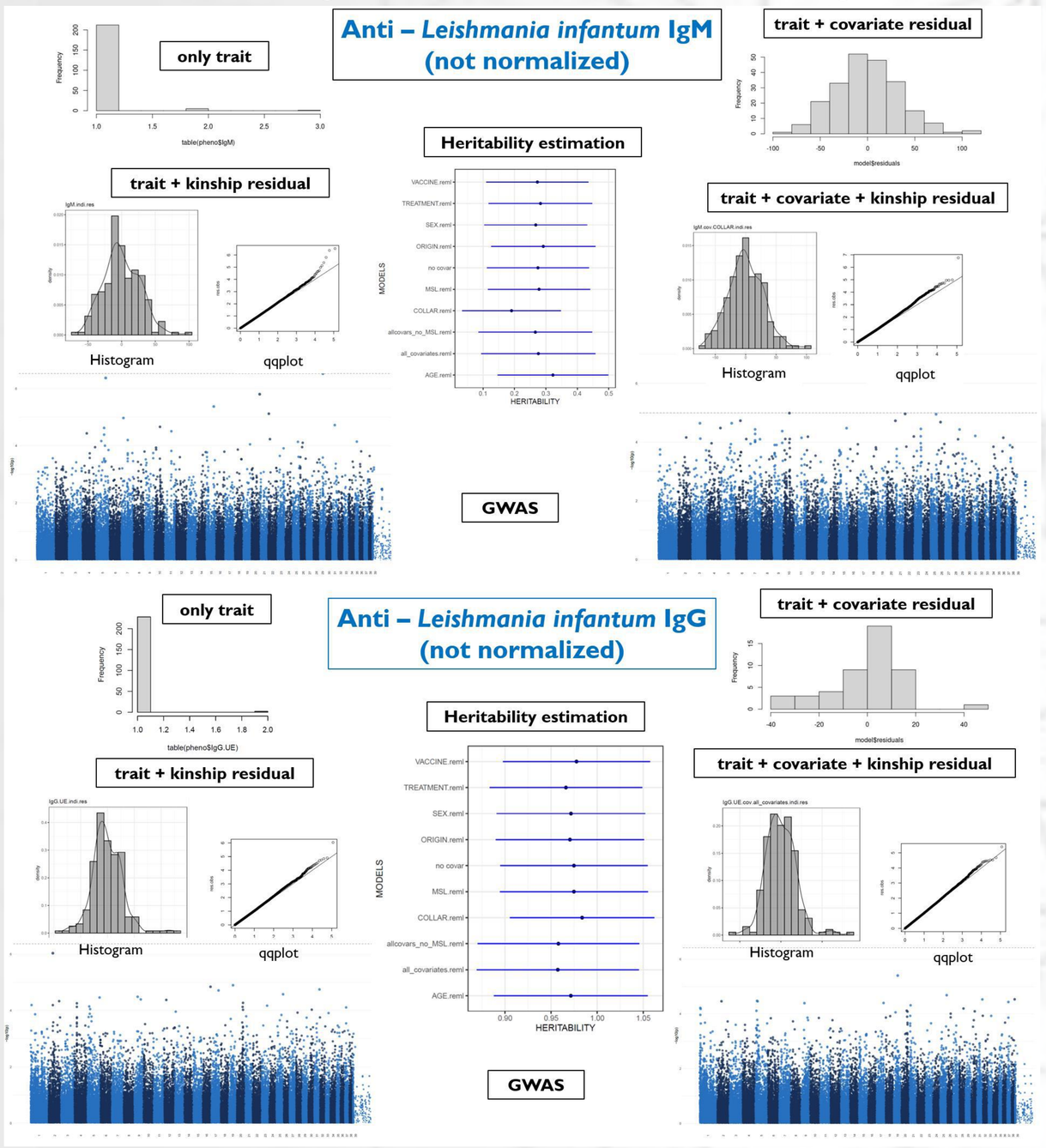
Mapping of candidate genes: 1 Mb upstream and downstream from the significant SNP based on annotation

RESULTS

Selection of models increased the accuracy on HA, GWAS and allowed the detection of large effect of DGB on clinical-immunological traits



Identification of candidate genes involved in innate immunity

Candidate Gene	Function	Trait
PTPN4	Phosphatase that negatively regulates TLR4-induced interferon beta production by dephosphorylating adapter TICAM2 and inhibiting subsequent TRAM-TRIF interaction.	*Anti-L. infantum* IgG
MD2	Encodes a protein which cooperates with TLR4 in the innate immune response to bacterial lipopolysaccharide (LPS), and with TLR2 in the response to cell wall components from Gram-positive and Gram-negative bacteria.	*Anti-L. infantum* IgM
IL17C	Cytokine that plays a crucial role in innate immunity of the epithelium, including to intestinal bacterial pathogens, in an autocrine manner. Stimulates the production of antibacterial peptides and pro-inflammatory molecules for host defense by signaling through the NF-kappa-B and MAPK pathways.	*Anti-L. infantum* IgM
IL6	Cytokine with is a potent inducer of the acute phase response. Rapid production of IL6 contributes to host defense during infection and tissue injury, but excessive IL6 synthesis is involved in disease pathology.	Clinical staging

CONCLUSION

The findings point to the predominance of the host genome effect on the clinical-immunological outcomes of the CVL and reveal a set of candidate genes that reinforce the role of innate immunity for resistance against *L. infantum*.

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