GENETIC FACTORS INVOLVED IN CANINE LEISHMANIASIS

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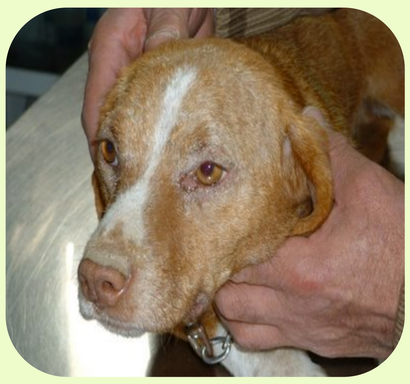
INTRODUCTION

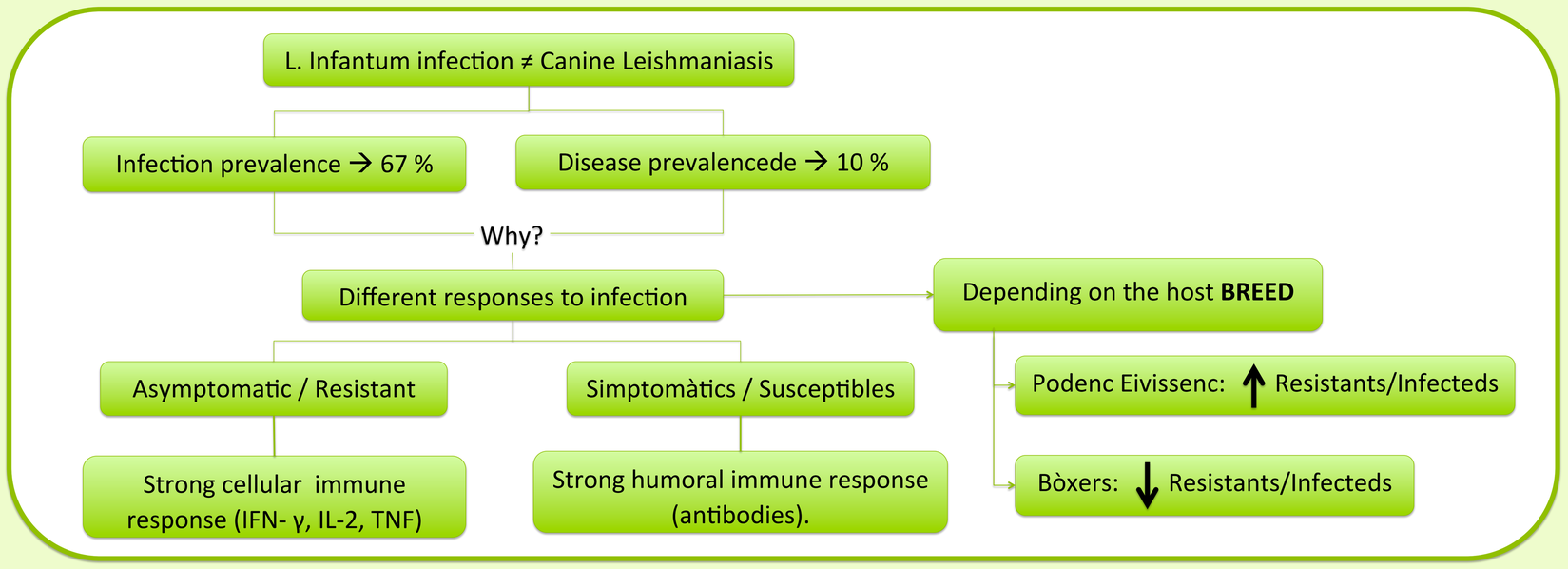
Leishmaniasis is a disease caused by more than 20 different species of **protozoan parasites** of the genus Leishmania which are transmitted from host to host through the bite of **sand flies**. **Visceral leishmaniasis** is caused mainly by L. infantum and it is the most severe form of human leishmaniasis, with an estimated incidence of 0.5 million new cases each year and more than 50,000 deaths a year. Dogs are the main reservoir of ***L. infantum*** all around the world and this parasite causes **Canine Leishmaniasis** to them.



Canine Leishmaniasis

- Sistemic disease
- Skin lesions
- Lymphadenopathies
- Weight loss
- Loss of appetite
- Ocular lesions
- Limp
- Renal disfunction
- Diarrea

OBJECTIVE OF THE REVIEW: Identifying the genetic factors that determine whether a dog is susceptible or resistant to Canine Leishmaniasis.



GENETIC ANALYSIS

Background

Rat Bcg/Ity/Lsh locus

- Resistance / susceptibility to leishmaniasis
- Regulation of the intrafagasomal parasite replication within macrophages
- Activation of macrophages
- Pleiotropic effects of antigen presentation

Gen Slc11a1

Solute Carrier family 11 member 1

- Chromosoma 37
- Total 9 kb
- 700 bp promoter
- 15 exons
- Microsatellite at intron 1

The Protein

- 547 AA
- 12 Transmembrane domains (TM)
- Consens transport sequence (TM8-TM9)
- Transportation of divalent metals outside the phagosome
- Control de la replicació dels patògens intracel·lulars.

Exon 11 deletion

- Elimination of a transmembrane domain (TM8)
- Elimination of the consensus sequence of transport
- Dysfunction of the protein
- Proliferation of the parasite within macrophages
- Susceptibility

Promoter variations

3 SNPs = 3 haplotypes
- TAA, TGA, CGA
- 3 transcription factors binding sites
- Alter the expression of Slc11a1

Rich G's region
- Polymorphism
- From 7-9 G's (8 is the most common)
- No independent association

Microsatellite in intron 1.
- 5 different alleles according to number of repetitions:
- 133, 137, 139, 141 and 145
- No independent association

Most frequent haplotypes

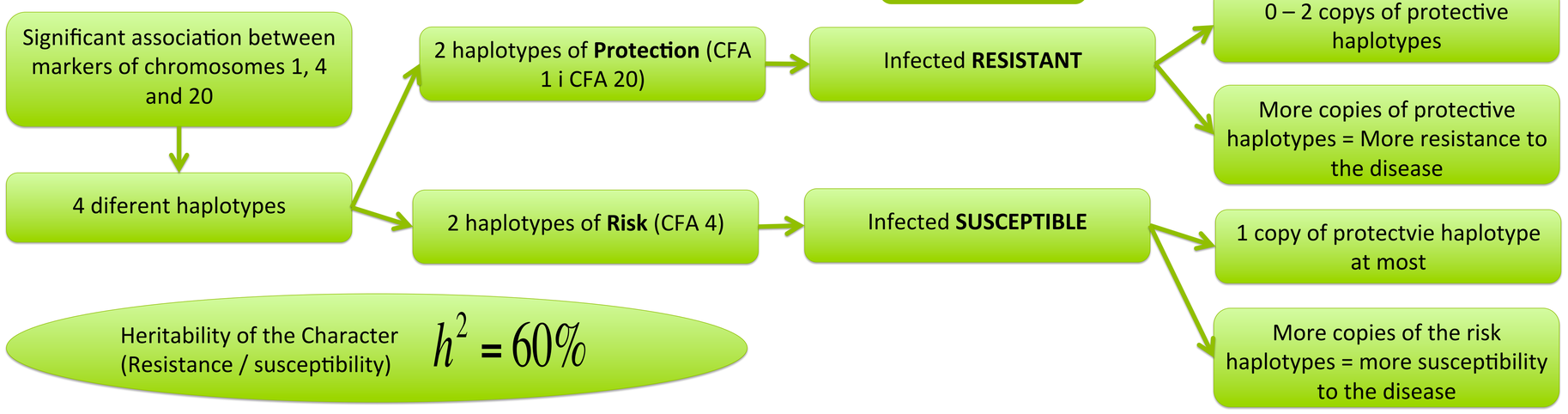
TAG-8-141 → Heterozygosity = Susceptibility in Bòxers (50% of cases)

TAG-9-145 → Homozygosity = Resistance in Bòxers (80% of controls)

The promoter of this gene plays a main role in the immune response against infection by Leishmania parasites. This region has binding sites for cytokines (INF-γ) that regulate gene expression of Slc11a1 during the activation of macrophages.

Figure 1. SNPs identified in the promoter region (539 bp) of the Slc11a1 canine gene are indicated in bold. Binding sites of transcription factors affected by any of the SNPs are indicated by a line above the consensus sequence. GR (glucocorticoid receptor); The site of EGFR (receptor site epidermal growth factor); Sp-1 (simian virus 40 protein-1). The rich G's region is underlined.

GWAS



GWAS problems

- Reduced sample size in most studies, low statistical power.
- No global significant association.
- The disease is very complex, it involves many genetic and biological factors. Difficult to find a single genetic cause.

CONCLUSIONS

- Slc11a1 canine gene analysis showed the association between haplotype 8-141-TAG and disease susceptibility in Boxer dogs, whereas homozygous haplotype 9-145-TAG seems to provide resistance.
- GWAS studies have reported an association of chromosomes 1, 4 and 20 with the disease and the presence of four different haplotypes, two involved in the development of resistance (chromosomes 1 and 20) and two in susceptibility (chromosome 4) .
- Although, studies have failed establishing a single major gene causing the disease, due to its great biological complexity.
- It is necessary to review the evidence found on this studies, because the poblations used in the case control studies are often small.

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