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Eprinomectin resistance in *Haemonchus contortus*: Phenotype, Genomic and Transcriptomic

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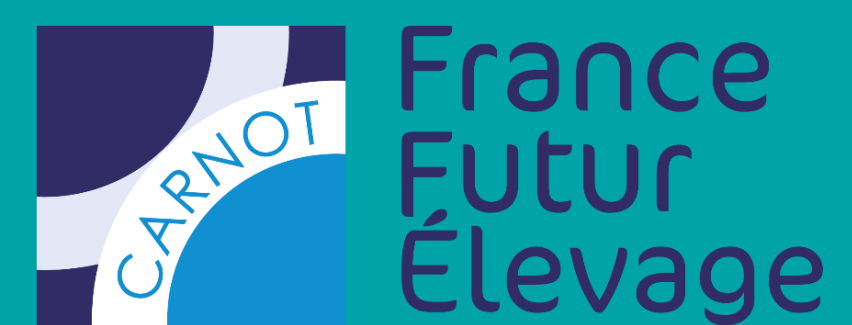
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Phenotype, Genomic and Transcriptomic

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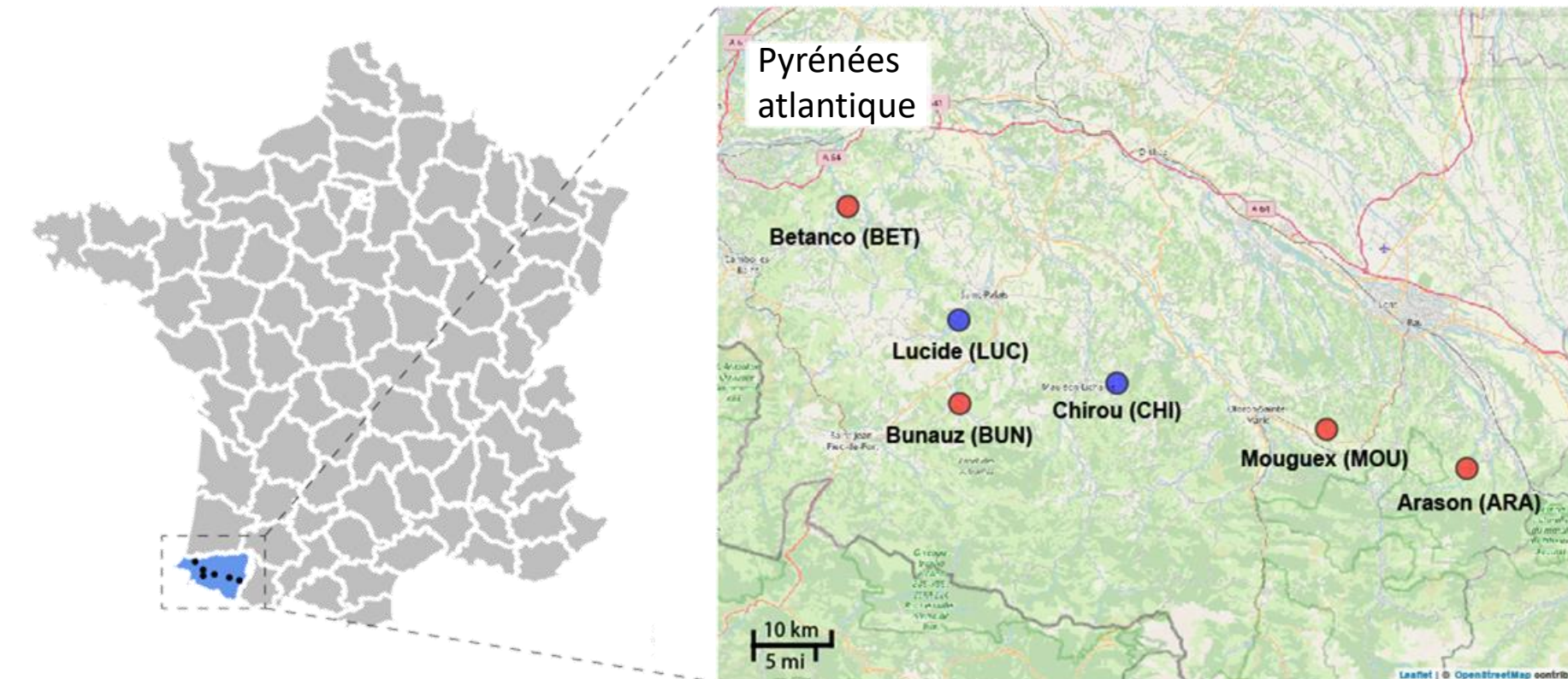
INTRODUCTION

Infections by gastrointestinal nematodes (GIN) in dairy sheep farms cause major economic losses and affect animal welfare. *Haemonchus contortus* is the most pathogenic GIN and dairy sheep are routinely treated with Eprinomectin (EPR) which is the last efficient Anthelmintic with no withdrawal period.

However, we recently reported eprinomectin-resistant isolates of *Haemonchus contortus* in 5 dairy sheep farms from the Pyrénées Atlantiques (Jouffroy, S. et al. *Parasitology* (2023)).

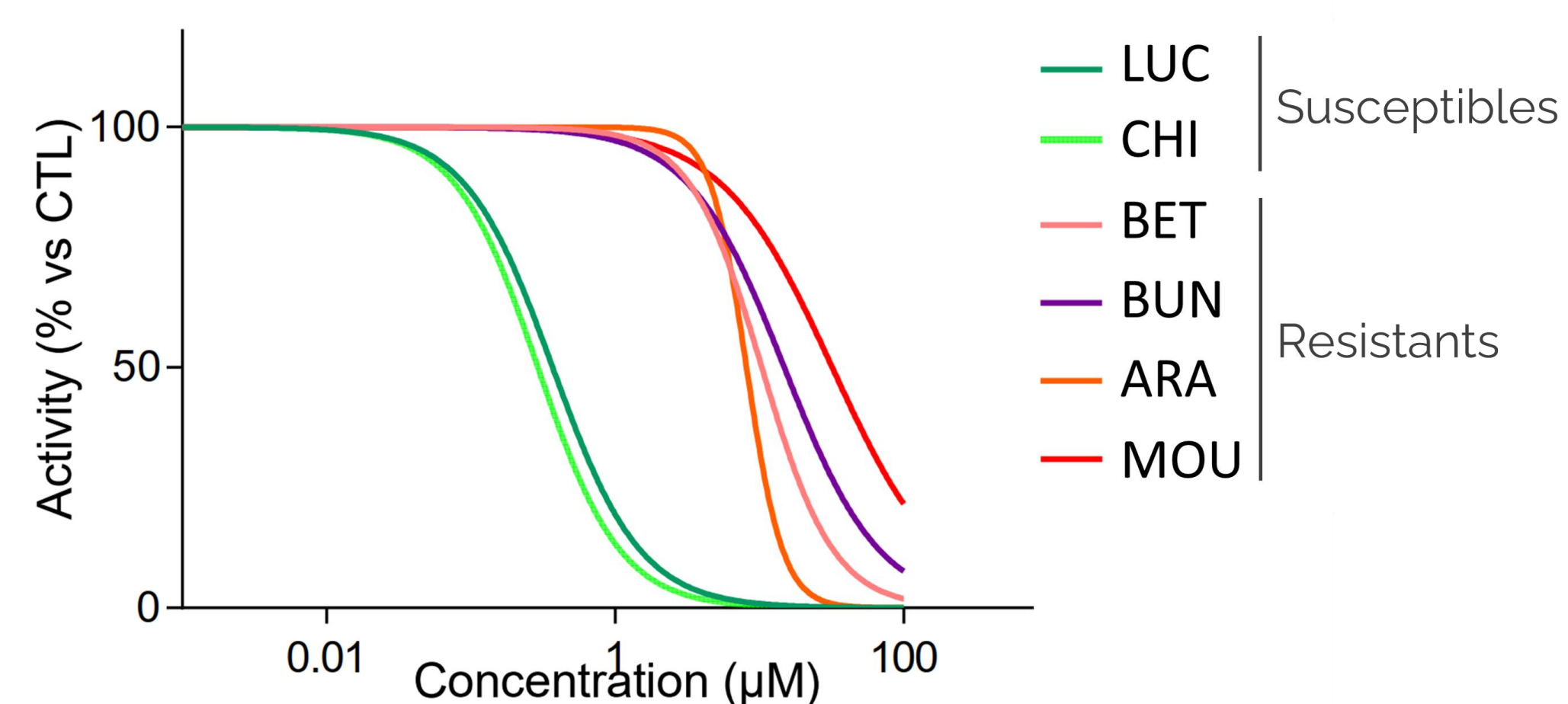
Objectives and Originality

By combining farm Anthelmintic treatment history with phenotypic, genomic and transcriptomic data, we aim at deciphering the determinant of Eprinomectin resistance and proposing resistant markers.



location of farms where different populations of *Haemonchus contortus* parasites were sampled

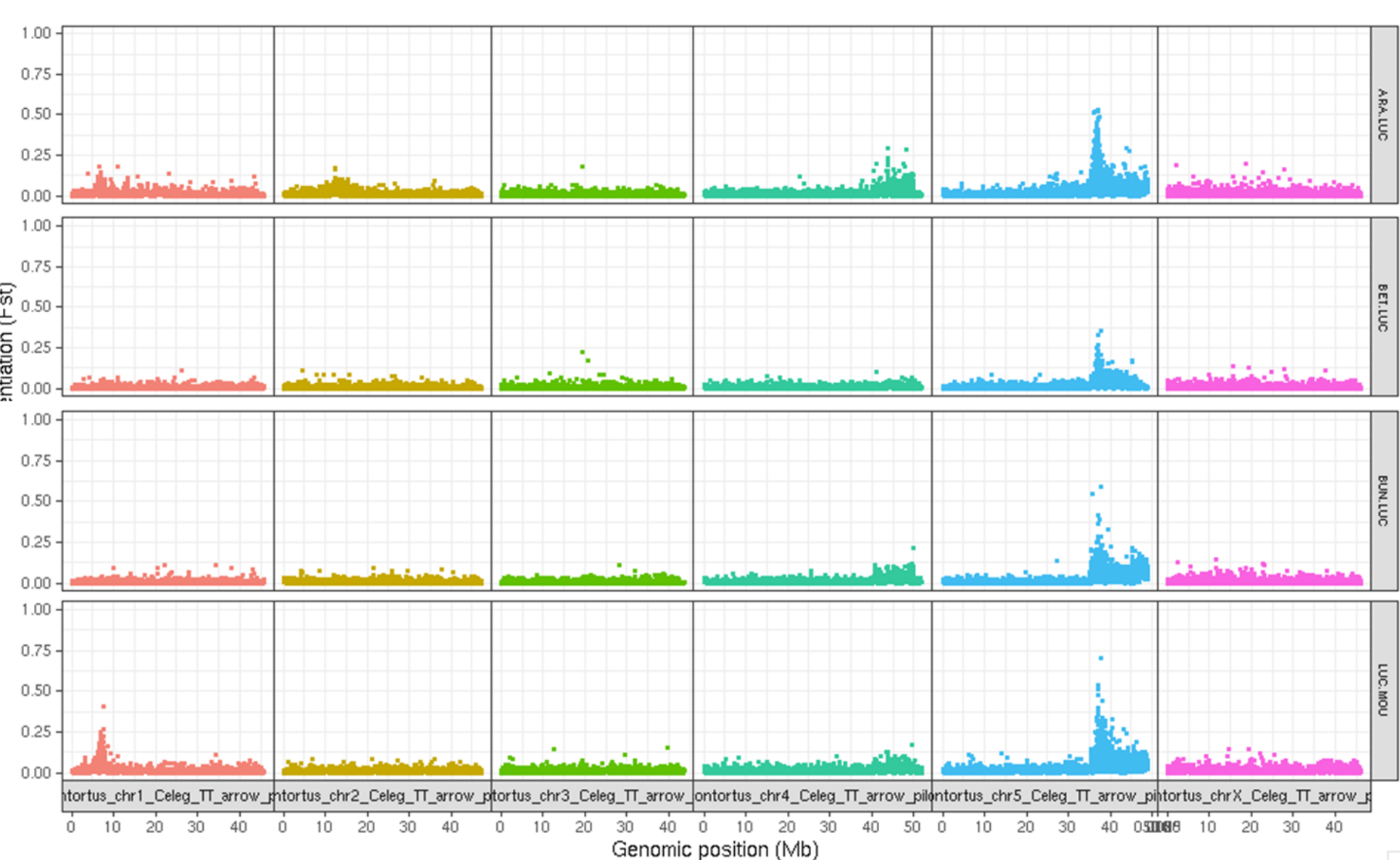
PHENOTYPIC CHARACTERIZATION



Resistance to EPR of field *Haemonchus contortus* populations is extremely high (>30x).

Motility of *H. contortus* larvae with increasing concentration of Eprinomectin (EPR), monitored with the WormicroTracker.

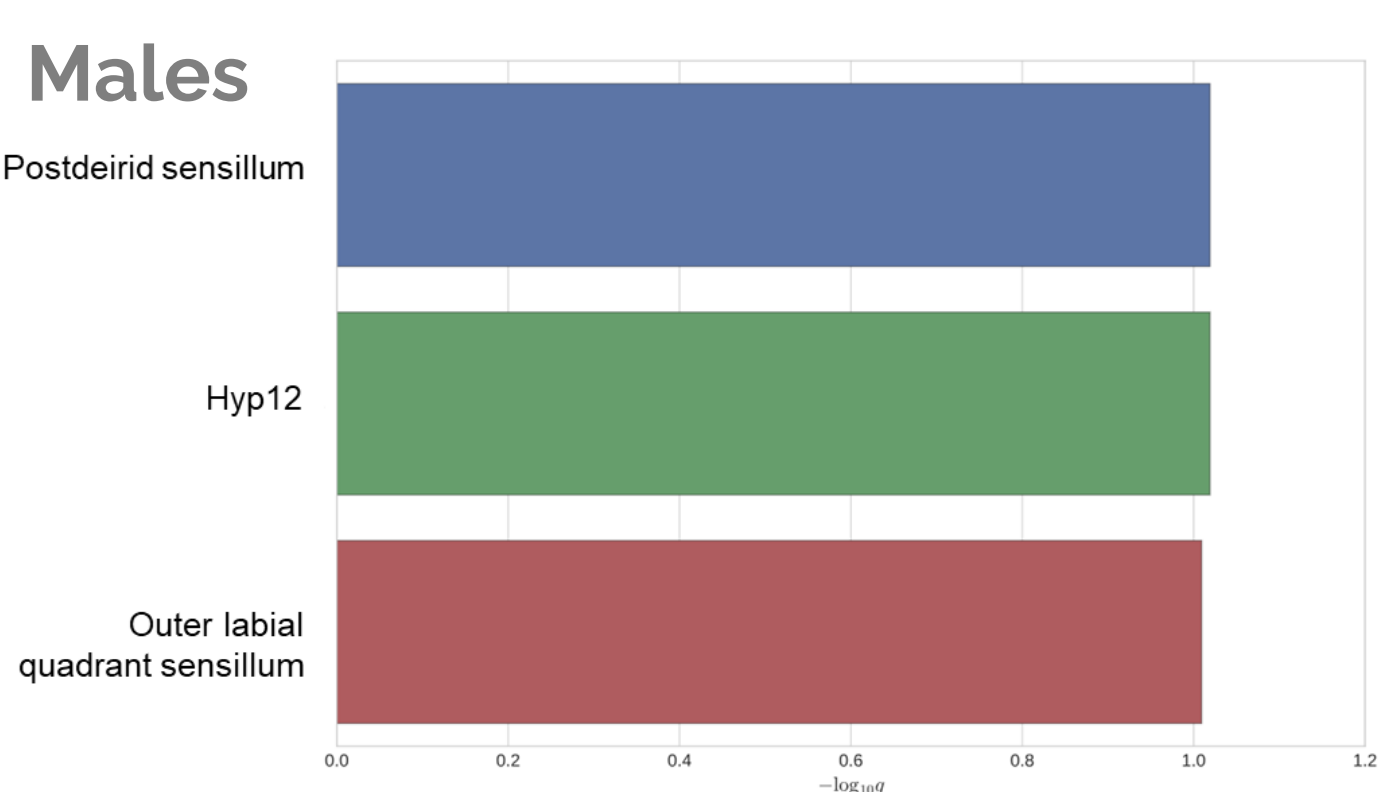
GENOMIC COMPARISONS



A major Quantitative Trait Locus (QTL) on chromosome V is associated to Eprinomectin resistance.

Genome-wide comparison of susceptible and Eprinomectin-resistant isolates. Pairwise genetic diversity (FST measured in 10 kbp windows using gredalF) between one susceptible isolates (CHI) and Eprinomectin-resistant isolates (ARA, BET, BUN, MOU)

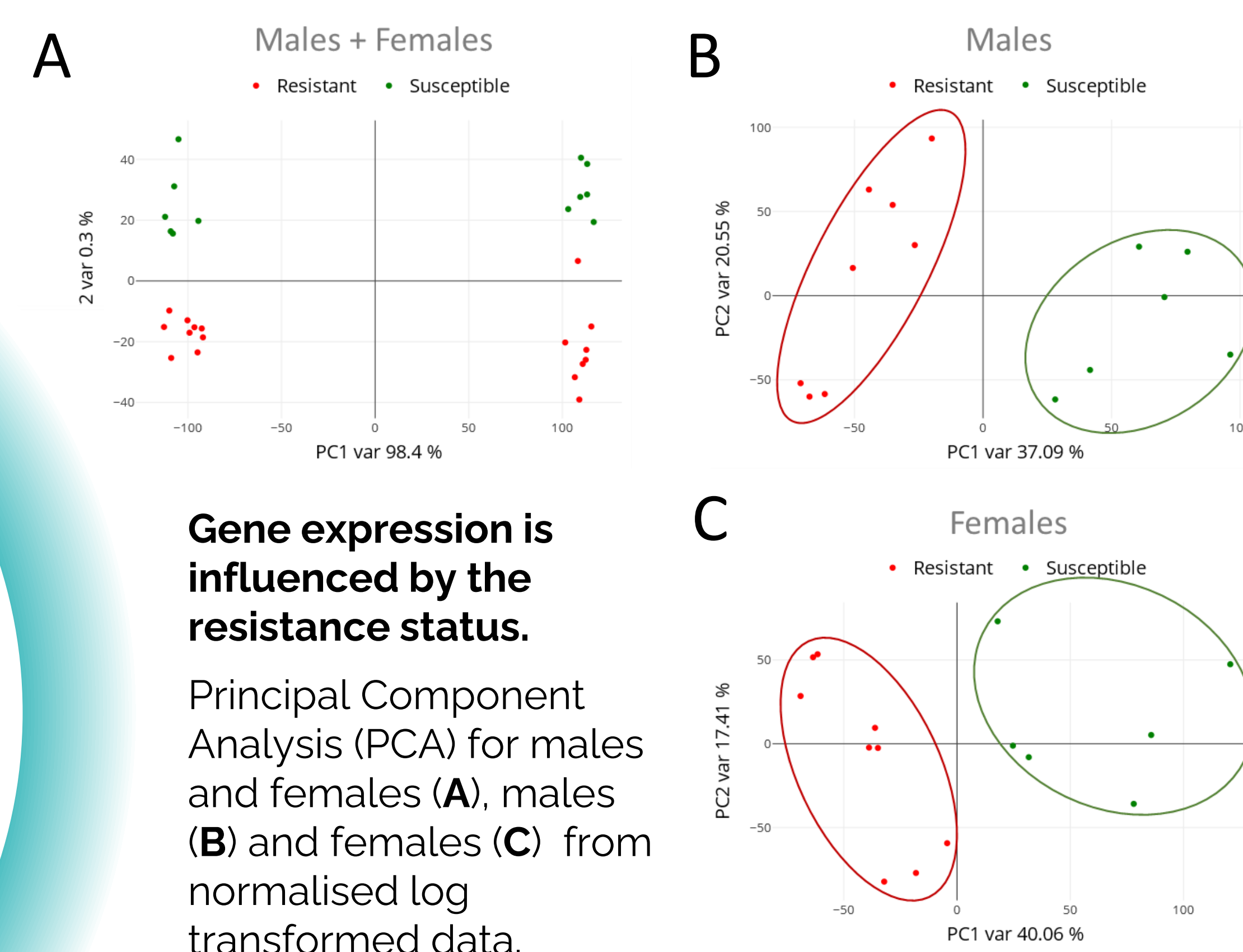
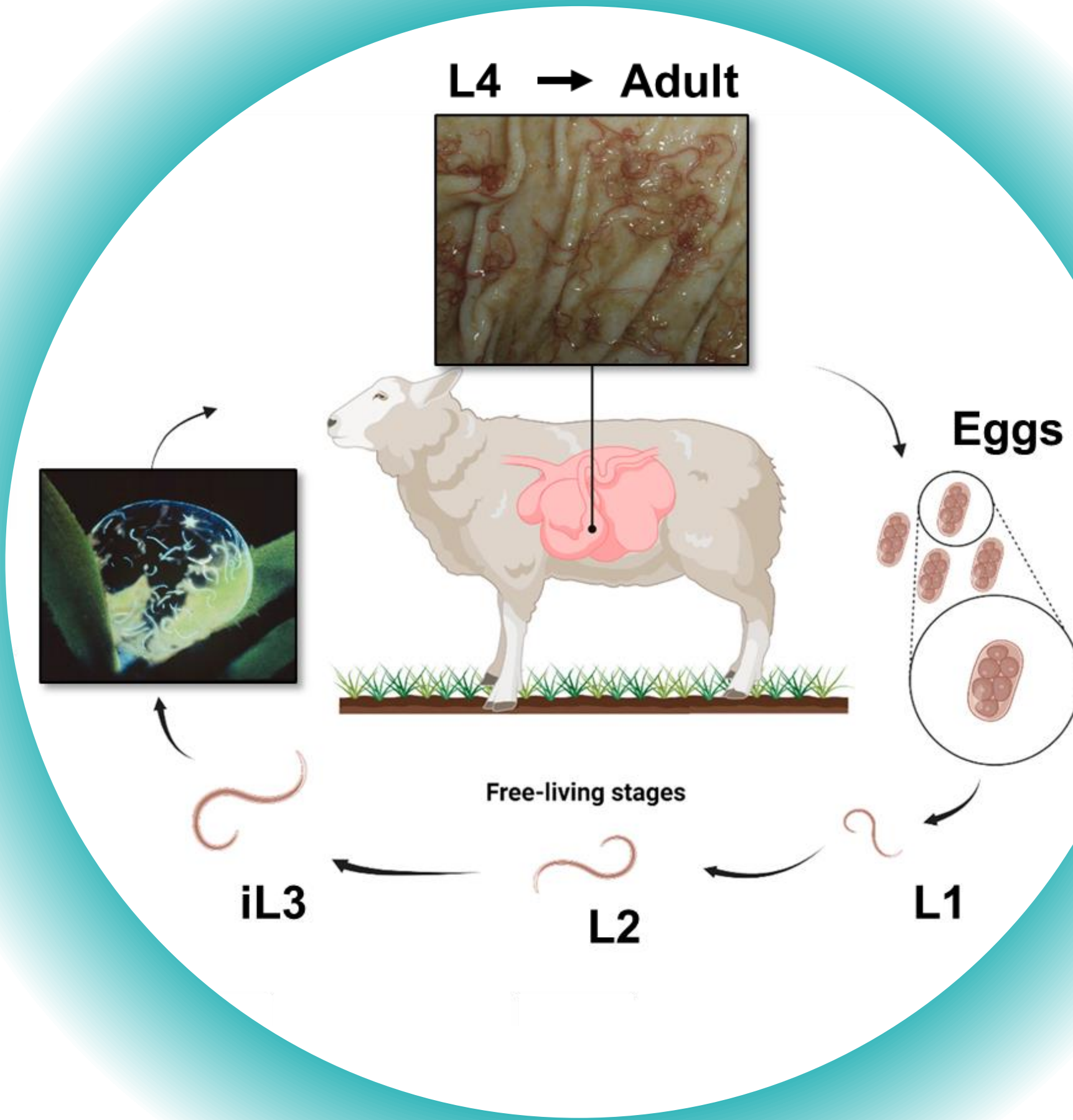
TISSUE ENRICHMENT



Enrichment analyses highlight the potential implication of neuronal tissues such as the sensillum (Tissue enrichment), of genes responding to anthelmintics in *C. elegans* (phenotype enrichment) and in diverse cellular and metabolic functions (Gene ontology enrichment).

C. elegans gene orthologs significantly differentially expressed between susceptible and resistant *Haemonchus contortus* populations and with a Fold change > 1.5 were taken to perform tissue and phenotypic enrichment with Wormbase enrichment analysis tool and gene ontology enrichment with Wormcat.

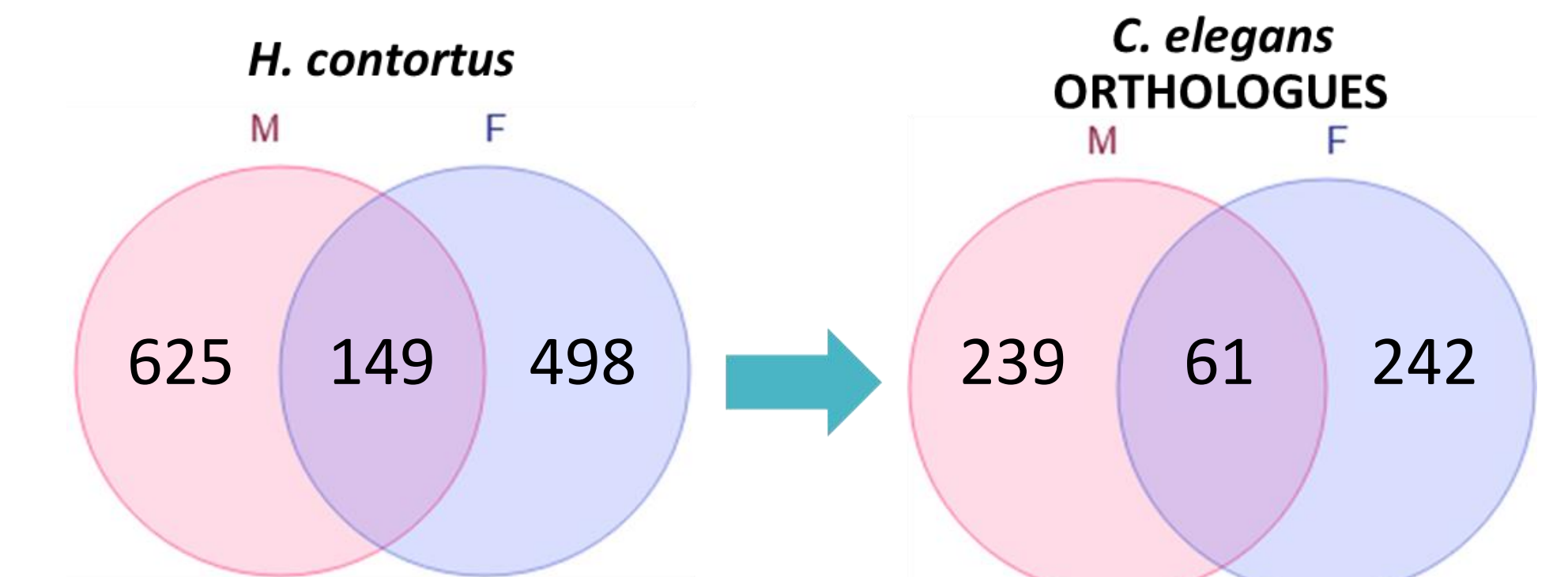
TRANSCRIPTOMIC ANALYSIS



Gene expression is influenced by the resistance status.

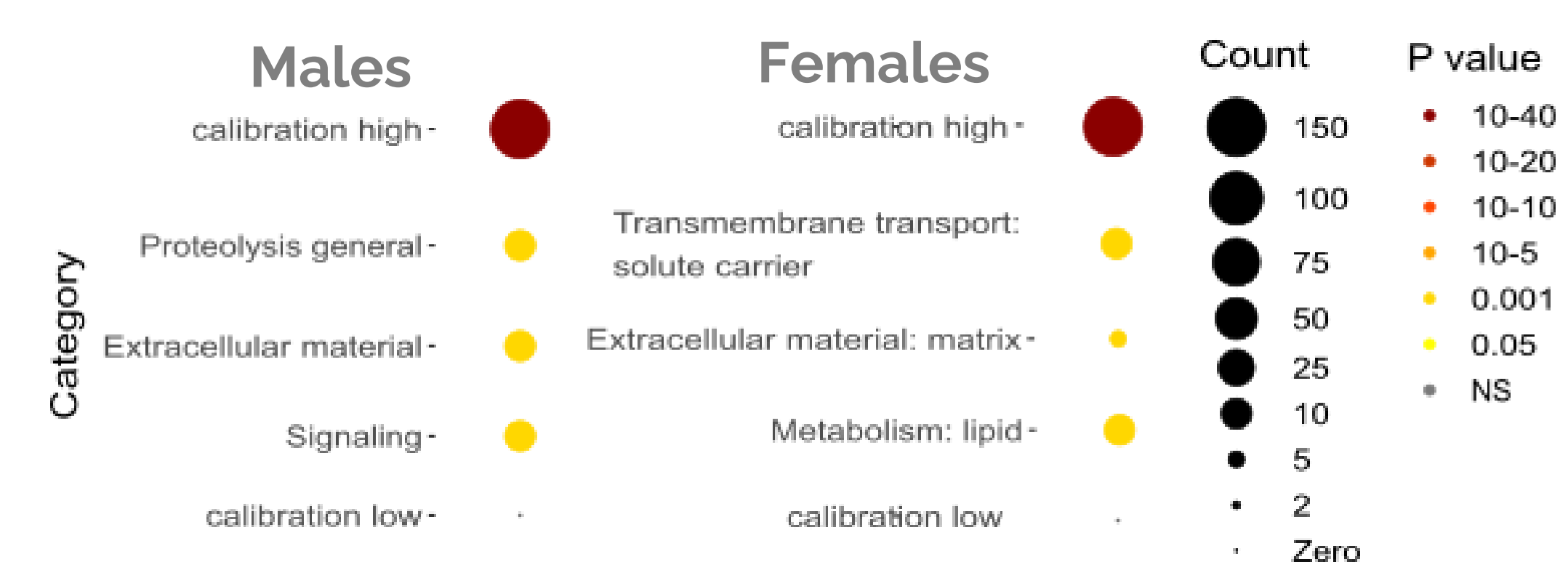
Principal Component Analysis (PCA) for males and females (A), males (B) and females (C) from normalised log transformed data.

DIFFERENTIALLY EXPRESSED GENES



Number of differentially expressed genes between susceptible and resistant males and females and their orthologs in *C. elegans*

GENE ONTOLOGY ENRICHMENT



CONCLUSION

Combining phenotypic, genomic and transcriptomic approaches enabled us to unveil the very high resistance to Eprinomectin of *Haemonchus contortus* isolates (>30x). These isolates selected a narrow QTL on chromosome V and genes expressed in neuronal tissues, associated with anthelmintic response and implicated in diverse cellular and metabolic functions. Investigations of individual genes deregulated and present on chromosome-V QTL are ongoing.