GENOMIC AND TRANSCRIPTOMIC ANALYSIS OF IVERMECTIN RESISTANCE IN *HAEMONCHUS CONTORTUS*

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Infections with parasitic nematodes are ubiquitous in grazing livestock throughout the world and are a major threat to global food security. Related nematodes cause debilitating diseases in billions of humans in some of the poorest countries in the world. Control of parasitic infections in animals and humans currently relies on mass drug administration of a limited number of anthelmintics. However, this is not sustainable due to the emergence and spread of anthelmintic resistance.

Haemonchus contortus is a highly pathogenic gastrointestinal nematode of small ruminants, which is becoming increasingly difficult to control due to multi-drug resistance. In the case of ivermectin, the mechanism(s) underlying resistance are poorly understood, with studies comparing resistant and sensitive parasites confounded by high levels of genetic diversity within and between and populations. To overcome this, we crossed a well-characterised multi-drug resistant isolate of *H. contortus* with a drug susceptible isolate to study ivermectin resistance while controlling for background variation. F2 adults were treated with ivermectin in vivo and pools of their L3 progeny pre and post treatment were sequenced. Bulk segregant analyses of these populations identified a major locus on chromosome V under ivermectin selection. This locus contains none of the previously studied 'candidate' resistance genes from the literature and no putative target genes, implicating a novel driver of resistance. Functional characterisation is ongoing in both *H. contortus* and transgenic *C. elegans* to identify which gene(s) in the locus confer ivermectin resistance. Transcriptomic analysis of the parental isolates and F2 adults with and without ivermectin treatment identified differential expression of a small number of genes associated with neuronal development or plasticity, including a

single gene within the chromosome V locus that is highly upregulated in geographically separated resistant populations. This gene has been the focus of our investigations so far.