

Genome-wide responses to macrocyclic lactone treatments in gastrointestinal nematodes of cattle

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The macrocyclic lactone (ML) drug family is the most widely used class of anthelmintic in animal health. Ivermectin, an avermectin, and moxidectin, a milbemycin, are structurally related but pharmacologically distinct compounds with similar therapeutic uses. Resistance in gastrointestinal nematodes to both drugs is now widespread across the livestock industry, but despite their extensive use, the genetic mechanisms underlying ML resistance remain poorly defined.

Using newly assembled chromosome-level reference genomes for *Ostertagia ostertagi* and *Cooperia oncophora*, the two most clinically significant gastrointestinal nematodes of cattle, we applied a genome-wide approach to identify evidence of selection following ML treatment in two field populations from Scotland. Faecal egg count reduction tests were conducted on dairy calves and larvae were collected pre- and post-treatment for pooled, mixed species, whole-genome sequencing. Appropriate filtering protocols were determined following an alignment of simulated reads from both species to each reference assembly and a combined assembly independently. We then identified species specific treatment-associated changes in allele frequencies, nucleotide diversity, and genetic differentiation across the genome.

Our analysis revealed genomic regions of differentiation on chromosomes 1, 3, and 5 in all *O. ostertagi* sample populations following treatment with either ivermectin or moxidectin. These findings provide novel insights into the genome-wide effects of ML selection in field populations of *O. ostertagi*. We further interpret these findings through comparison with previously identified QTLs of related GINs: *Haemonchus contortus* and *Teladorsagia circumcincta*.