IJP: Drugs and Drug Resistance 8 (2018) 70–80

Contents lists available at ScienceDirect

IJP: Drugs and Drug Resistance

journal homepage: www.elsevier.com/locate/ijpddr

P-glycoprotein-9 and macrocyclic lactone resistance status in selected strains of the ovine gastrointestinal nematode, *Teladorsagia circumcincta*

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ARTICLE INFO

Keywords:
Teladorsagia circumcincta
Anthelmintic resistance
P-glycoprotein
Ivermectin

ABSTRACT

The *Teladorsagia circumcincta* P-glycoprotein-9 (*Tci-pgp-9*) gene has previously been implicated in multiple-anthelmintic resistance in this parasite. Here we further characterise genetic diversity in *Tci-pgp-9* and its possible role in ivermectin (IVM) and multi-drug resistance using two UK field isolates of *T. circumcincta*, one susceptible to anthelmintics (MTci2) and the other resistant to most available anthelmintics including IVM (MTci5). A comparison of full-length *Tci-pgp-9* cDNA transcripts from the MTci2 and MTci5 isolates (~3.8 kb in both cases) indicated that they shared 95.6% and 99.5% identity at the nucleotide and amino acid levels, respectively. Nine non-synonymous SNPs were found in the MTci5 sequences relative to their MTci2 counterparts. Twelve genomic sequence variants of the first internucleotide binding domain of *Tci-pgp-9* were identified and up to 10 of these were present in some individual worms, strongly supporting previous evidence that amplification of this gene has occurred in *T. circumcincta*. On average, fewer distinct sequence variants of *Tci-pgp-9* were present in individual worms of the MTci5 isolate than in those of the MTci2 isolate. A further reduction in the number of sequence variants was observed in individuals derived from an IVM-treated sub-population of MTci5. These findings suggest that *Tci-pgp-9* was under purifying selection in the face of IVM treatment in *T. circumcincta*, with some sequence variants being selected against.

1. Introduction

The control of parasitic nematodes of ruminants, such as *Teladorsagia circumcincta,* currently relies heavily on the use of anthelmintic drugs, and this has led to widespread selection for drug resistance. Anthelmintic resistance in *T. circumcincta* has been documented in most countries where this parasite occurs (Kaplan, 2004) and it has been reported in UK field populations against three of the five major classes of anthelmintics. Resistance to single and multiple classes of anthelmintic has frequently been diagnosed in populations of this species, with 'triple-resistance' (i.e. resistant to benzimidazoles (BZs), imidothiazoles and macrocyclic lactones (MLs)) being reported in *T. circumcincta* isolates from sheep in Europe more than a decade ago (Sargison et al., 2001). Although as yet there have been no reported field cases in the UK of resistance to the amino-acetonitrile derivative class of anthelmintics, which includes Monepantel, monepantel-resistance has been observed in *T. circumcincta* under experimental conditions (Bartley et al., 2015). Disturbingly, monepantel-resistance has been reported in field populations of *T. circumcincta* (and *Trichostronglus colubriformis*) from sheep and goats in New Zealand (Leathwick et al., 2013; Scott et al., 2013) and in *Haemonchus contortus* in sheep in Australia (Sales and Love, 2016) and in the Netherlands (Van den Brom et al., 2015).

Anthelmintic resistance in most cases is accepted as a pre-adaptive phenomenon (Jackson and Coop, 2000) in which the genes responsible for resistance already exist at a low frequency within a population but become dominant under drug selection. Anthelmintic resistance has been attributed to several genetic factors including qualitative and/or quantitative changes in putative drug targets (e.g. glutamate-gated chloride channels and β-tubulin), and members of the adenosine triphosphate (ATP)-binding cassette (ABC)-transporter superfamily (P-glycoproteins (Pgps), multi-drug resistant proteins and half-transporters) have also been implicated (Xu et al., 1998; Prichard and Roulet, 2007; James and Davey, 2009; Dupuy et al., 2010). Pgps have been implicated in the molecular basis of IVM-resistance in *H. contortus* (Xu et al., 1998; Molento and Prichard, 2001), and polymorphisms in certain alleles have the potential to improve drug efflux from the cell, thereby changing the drug distribution within the parasite's tissues and preventing anthelmintics reaching their site of action (Wolstenholme et al., 2004; Prichard and Roulet, 2007). Studies in which IVM or

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https://doi.org/10.1016/j.ijpddr.2018.01.004
Received 17 August 2017; Received in revised form 15 January 2018; Accepted 17 January 2018
Available online 31 January 2018
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Fig. 1. Amino Acid Sequence of *Tci-pgp-9*

Amino acid sequences from the UK isolates MTci2 and MTci5, aligned with sequence information derived from two near-isogenic strains of *T. circumcincta* from NZ. The first of the NZ strains (NZ-S) was known to be susceptible to all available anthelmintics while the second (NZ-R), which shared a largely common genetic background, was multiple-anthelmintic resistant. Sequence motifs are underlined and annotated above the sequence. The positions of inter-nucleotide binding domains A and B (*IBDA* and *IBDB*) are underlined and annotated below the sequences. Highlighted in yellow are six residue substitutions identified in the UK isolates (numbered 1–6), and four previously identified residue substitutions in NZ isogenic strains (annotated A-D).

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