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Research paper

# Salivary IgA: A biomarker for resistance to *Teladorsagia circumcincta* and a new estimated breeding value

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ABSTRACT

*Teladorsagia circumcincta* is the dominant nematode of sheep in cool, temperate climates. Faecal nematode egg counts (FEC) are widely used to identify the intensity of infection and as a measure of host resistance to nematodes. However due to density-dependent effects on worm fecundity the relationship between FEC and worm burden is not linear. In addition collecting FEC data is challenging on a practical level and there is a need for more reliable markers of resistance. There are two major known mechanisms of immunity to *T. circumcincta*: IgE against third stage larvae (L3) and IgA against fourth stage larvae (L4), which inhibits parasite growth. In this study salivary IgA responses were measured in over 5000 animals against L3 antigen by Enzyme Linked Immunosorbent Assay (ELISA). Antigen-specific IgA levels were negatively correlated with FEC ($r = -0.26$, $SE = 0.02$) and were heritable ($h^2 = 0.16$, $SE = 0.04$) indicating that they can be used to identify resistant animals suitable for inclusion in selective breeding programs. Antigen-specific IgA responses were not negatively correlated with muscle depth. Our analyses indicate that selection for *T. circumcincta* L3 antigen-specific IgA is possible without impacting on the production traits for the Lleyn breed.

## 1. Introduction

Infection with gastro-intestinal strongyles such as *Teladorsagia circumcincta* presents a significant problem to the sheep breeding industry, impacting both the welfare and productivity of animals. Anthelminthics are commonly used to control helminth infection but reliance on this method alone is ill-considered in light of growing anthelminthic resistance (Traversa and von Samson-Himmelstjerna, 2016). An integrated approach to ensure sustainable control strategies for the future is the main objective of research in this area and requires improved phenotypic and genetic markers of resistance and resilience to inform selective breeding programs (Jackson et al., 2009).

Whilst both resistance and resilience contribute to control of helminth infection it may be more preferable when considering productivity to select for resilient sheep that can better tolerate the infection and grow in spite of worm burden. Previous research has demonstrated that there are two main mechanisms of immunity to *T. circumcincta* infection. Immunoglobulin E (IgE) against third stage larvae (L3), which inhibits larval establishment and Immunoglobulin A (IgA) against fourth stage larvae (L4), which inhibits parasite growth (Lee et al., 2011; Martinez-Valladares et al., 2005; Murphy et al., 2010; Strain et al., 2002). The IgE response, although protective is associated with pathology that leads to a relative protein deficiency in the animal (Stear et al., 2003). Thus resistance to the infection is costly both in terms of welfare and productivity. The IgA response impairs the growth of the worms resulting in shorter and crucially less fecund worms that contribute less to pasture contamination (Stear et al., 1995; Strain et al., 2002). IgA without the pathology and negative impact on animal growth associated with IgE has potential as a marker of resilience.

Traditionally low faecal nematode-egg count (FEC) is used as a marker of resistance in selective breeding programmes. However, mathematical modelling indicates that IgA has advantages over FEC as a selection tool; after 7 generations of selection based on plasma IgA a drop in FEC of 85% was achieved whereas selection on FEC alone gave only a 50% reduction (Prada Jimenez de Cisneros et al., 2014b). There are also other disadvantages of using FEC as a measure of infection intensity; worm density-dependent effects on egg production mean that high worm burdens do not always tally with high FEC (Bishop and

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Stear, 2000; Romeo et al., 2014; Smith et al., 1987), sampling per rectum is invasive and often samples can't be obtained. Measuring IgA in plasma is also invasive and requires specialist training.

Salivary IgA to a carbohydrate larval antigen (CARLA) has been used successfully to measure immunity to gastrointestinal nematodes (Shaw et al., 2012). Here an Enzyme Linked Immunosorbent Assay (ELISA) was developed to measure *T. circumcincta*-specific IgA in saliva. The test measures the IgA response to L3 larvae with the rationale that resistance results from the recognition of multiple antigens (Ellis et al., 2014). This test is deliberately targeted to the predominant nematode infection in the UK and other temperate climates. Breeders and veterinarians have readily adopted this test and results are reported as an Estimated Breeding Value (EBV) for inclusion in the selective breeding programmes of the Lleyn Performance Recording group.

## 2. Material & methods

### 2.1. Animals and sample collection

Eighteen farms owned by Performance Recorded Lleyn Breed Society members throughout the UK were involved in the study and bred all the Lleyn animals that were tested (n = 5201). Sampling was undertaken between the months of July–September to coincide with exposure to *Teladorsagia circumcincta* through grazing. For lambs sampled between 2014 and 2017 the average age at sampling was 193 days-of-age. The age distribution of animals in the study is shown in Fig. 1.

Saliva samples were collected by insertion of a dental swab (Robinson Healthcare, 12 mm), secured by forceps, into the cheek pouch of the animal. Swabs were sealed in 15 ml falcon tubes and saliva recovered by centrifugation at 449 rcf for 5 min. Saliva was then frozen at −20 °C before use in ELISA.

### 2.2. Antigen and ELISA

*T. circumcincta* antigen was prepared by homogenisation of 1 million L3 in 10 mM Tris − HCL with addition of protease inhibitors (0.5 M EDTA, 0.5 M EGTA, 1 M NEM, 0.33 M PMSF, 0.1 M TPCK, 1 mM pepstatin) and 2% sodium deoxycholate. Homogenisation was performed at 30 Hz for 6 min. in a Retsch MM400 mixer mill. Antigen was passed through a 0.2 µm syringe filter and frozen before use in ELISA.

Antigen-specific salivary IgA ELISA: 96 well BD Falcon ELISA plates were coated with 5 µg/ml L3 antigen diluted in 0.06 M carbonate buffer (0·04 M NaHCO3, 0·02 M NaCO3, pH9·6) and incubated overnight at 4 °C. Non-specific binding was blocked with 4% Marvel milk powder in Phosphate-buffered saline with 0·1% Tween 20 (PBST) for 2 h at 37 °C. Wells were washed three times in PBST after each subsequent step. Saliva samples were added at 1:4 dilution using PBST as a diluent and incubated for 30 min at 37 °C. Isotype-specific detection antibody horseradish peroxidase conjugated rabbit anti-ovine IgA (AbD serotec AHP949 P) was added at 1:15 000. Plates were incubated for 30 min at 37 °C. An additional wash in distilled water was carried out before developing with 3,3′, 5,5′-tetramethylbenzidine (TMB) peroxide substrate (Pierce™), at room temperature for 5 min. Optical density (O.D.) was read at 450 nM using a spectrophotometer. Results were expressed as an O.D. Index calculated as (sample O.D. – control O.D.)/ (high-responder O.D. – control O.D.). This O.D. Index and animal pedigree were used to generate an estimated breeding value for antigen-specific IgA (IgA EBV).

To ensure standardisation of IgA responses from year to year the high responder pool was created from 6 to 10 sheep and this provides enough material to test thousands of animals. When a new batch of high responder pool is created the reactivity of the previous pool and the new pool are carefully compared by testing multiple samples with both batches.

### 2.3. Calculation of IgA estimated breeding value (EBV)

At the time of producing IgA EBVs, raw antigen-specific IgA data were available for 5201 Lleyn animals, measured between 2014 and 2016 from 15 flocks. Basic data edits were undertaken to remove data for animals that were sampled multiple times or outside of 100–350 days of age. To normalise the IgA phenotype distribution a Box-Cox procedure was applied using a square root transformation and extreme outliers removed. To allow genetic parameter estimation with the other traits routinely evaluated in the national Lleyn genetic evaluation, Faecal Egg Count (FEC) (log transformed), birth weight (kg), 8 week weight (kg), 21 week weight (kg), ultrasound muscle depth (mm), ultrasound fat depth (mm) and ewe weight at tupping (kg) were extracted from the genetic evaluation database for the flocks that recorded antigen-specific IgA. For genetic parameter estimation, animals that were fostered, the result of embryo transfer, not purebred or from a litter size greater than 3 were removed from the dataset. Any record which was part of a small (< 5 animals) or single sire contemporary group were set to missing, as were records outside 3 standard deviations from the contemporary group mean.

Contemporary groups (CG) were as defined in the routine national genetic evaluations (Ceyhan and Mrode, 2015). For birth- and 8 week-weight the CG was defined as flock of birth, season and sex (Flock-Season-Sex CG). The same definition, but with the inclusion of a user defined management group (Flock-Season-Sex-Managementgroup CG) was used for 21 week weight, ultrasound muscle and fat depth and Faecal Egg Count. In all cases, season was based on date of birth and within year (defined from August to July) was sliced so that consecutive animals were not more than 28 days apart in age and the total time span

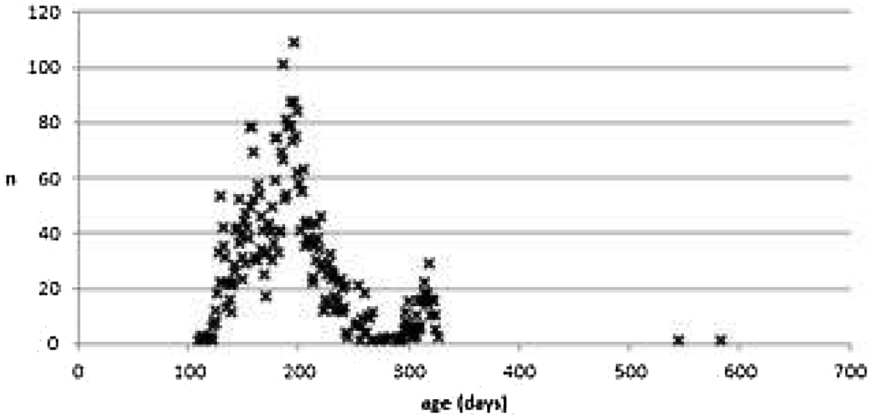


**Fig. 1.** Age distribution of animals sampled between 2014 and 2017. Animals greater than 350 days old were excluded from final analysis. The mean age at sampling for all animals was 193 days. For males the mean age was 182 days and for females 196.

of a CG was not more than 155 days (5.5 months). The CG for ewe weight at tupping was the herd and year of tupping (Tupping herd-year CG). For IgA it was decided to use a similar CG as for 21 week weight, ultrasound scans and FEC, however including the IgA management group. A five generation pedigree was built for animals with phenotype information.

For both parameter estimation and the calculation of EBVs the statistical models used for routine genetic evaluation were used for all traits other than IgA. The statistical models fitted were as follows;

Birth weight = Flock-Season-Sex CG + litter size born + dam age + animal genetic effect + dam genetic effect + permanent environment effect

8 week weight = Flock-Season-Sex CG + litter size reared + dam age + animal genetic effect + dam genetic effect + permanent environment effect

21 week weight / ultrasound muscle depth /ultrasound fat depth / FEC = Flock-Season-Sex-Managementgroup CG + litter size reared + dam age + scanning age + Flock-Season-Sex-Managementgroup CG * scanning age + animal genetic effect

Ewe weight at tupping = Tupping herd-year CG + animal genetic effect

The CG, litter size and dam age terms were fitted as fixed class effects. CG was as defined above, litter size born was the number of lambs born in the same litter, litter size reared was the number of lambs born and raised in the same litter. Dam age was the age of the dam in years, with dams over 5 years-of-age being recorded as 5 yrs.

Scanning age was the age of the animal at the time of the 21 week weight and ultrasound scans were measured. It is recorded in days and was fitted in the model as a fixed covariate.

Fitted as random effects were the additive, dam and permanent environment genetic effects.

The final statistical model for IgA was as follows;

IgA = Flock-Season-Sex-ManagementGroup CG + litter size born + age when IgA sample taken + animal genetic effect

Model terms were fitted in the same manner as above, with age at IgA sample being recorded in days and fitted as a fixed covariate.

ASReml (Gilmour et al., 2009) was used to estimate genetic parameters to produce EBVs. To estimate (co)-variance components, a series of uni- and bi- variate animal models (described above) were fitted. The software MiX99 (Lidauer et al., 2011) was used to produce EBVs based on the variance components estimated and the models described above.

## 3. Results

After basic data edits antigen-specific IgA records were available for 5188 animals, of which 4473 also had FEC records available in the national Lleyn genetic evaluation. Table 1 describes the raw data that was available for genetic parameter estimation. A small to moderate heritability of 0.16 (0.04) was estimated for antigen-specific IgA transformed to a normal scale (Table 2), this was double that of the heritability calculated for FEC in the same cohort (Table 2). In addition to being heritable, there was sufficient genetic variation to enable selection of animals for increased antigen-specific IgA activity.

**Table 1**
A summary of the edited Lleyn data used to estimate genetic parameters.

| Trait | n | average | min | max | Std. dev |
|---|---|---|---|---|---|
| birth weight (kg) | 66,626 | 4.14 | 2.0 | 7.0 | 0.96 |
| 8 week weight (kg) | 268,594 | 19.17 | 5.7 | 32.8 | 4.36 |
| 21 week weight (kg) | 102,035 | 35.76 | 13.0 | 58.6 | 7.44 |
| Ultrasound muscle depth (mm) | 63,499 | 24.08 | 13.7 | 34.5 | 3.41 |
| Ultrasound fat depth (mm) | 62,825 | 2.60 | 0.1 | 7.13 | 1.36 |
| ewe weight at tupping (kg) | 13,398 | 54.71 | 20 | 90 | 12.12 |
| Faecal egg count – Strongyles (log transformed) | 5,840 | 5.12 | 0.0001 | 9.00 | 2.08 |
| Faecal egg count – Nematodirus (log transformed) | 5,840 | 1.89 | 0.0001 | 7.62 | 2.36 |
| transformed IgA | 4,622 | 0.71 | 0.03 | 1.99 | 0.35 |

Genetic relationships estimated from bi-variate analysis are reported in Table 2. Moderate genetic correlations between IgA and FEC were estimated with a negative correlation (−0.26 (0.02)) between IgA and FEC Strongyles. These correlations indicate that as IgA increases genetically, FEC Strongyles decreases improving host resistance for these types of worms. A positive correlation (0.27 (0.19)) between IgA and FEC Nematodirus was also observed, however this correlation estimate was not significantly different from 0.

Parameters were unable to be estimated for birth and eight week weight due to convergence issues. The correlations between antigen-specific IgA activity and production traits were not significantly different from 0.

Based on the genetic parameters estimate, EBVs were produced for IgA with the only correlation fitted for IgA being with FEC Strongyles (−0.26 (0.02)). The average IgA EBV was 0.00 and ranged between −0.17 and 0.18 with a standard deviation of 0.01. A simple correlation between sire EBV and progeny IgA was undertaken for sires with more than 10 progeny recorded for IgA. After adjusting the phenotypes for the fixed effects fitted in the statistical model, a correlation of 0.91 was observed (Fig. 2).

## 4. Discussion

This study has shown that antigen-specific salivary IgA responses are heritable and negatively correlated with FEC making them suitable to identify animals resistant to nematodes for use in selective breeding programs. The relationship between sire EBV and progeny IgA suggests that sires with higher EBVs for IgA will produce offspring with genetics to produce higher IgA responses. Antigen-specific IgA responses have twice the heritability of FEC (which is currently used to identify resistant animals) suggesting that selection based on IgA would be more efficient. Furthermore the model predicts there would be no adverse effect of selection on production traits (correlations between antigen-specific IgA and fat and muscle deposition were not significantly different from zero). This is in contrast to ecological theory which predicts that a trade-off between immunity and host-growth will exist due to competing energetic needs (Klasing, 2004). It is possible that this trade-off is not evident for the measures of immunity and growth used here because the IgA response to *T. circumcincta* is not known to cause pathology and a relative protein deficiency as is the case for the IgE response (Stear et al., 2003).

Previous research has focussed on plasma IgA responses to *T. circumcincta* L4 antigens (Prada Jimenez de Cisneros et al., 2014a; Strain et al., 2002). Here L3 antigens were used, as they are easier and less costly to produce than L4 sourced antigens. There is good evidence that L3 antigens can be used as a proxy for L4 (McRae et al., 2014) and a strong correlation between plasma IgA responses to L3 and L4 antigens has previously been shown (Stear et al., 1995). Despite being easier to produce it is likely that responses to L3 antigens will have weaker relationships to FEC and perhaps productivity than L4 and in the future the use of L4 antigens or a suite of L4 recombinant antigens in ELISA may be advantageous. Indeed the heritability of IgA activity to L4 antigens in plasma of Scottish Blackface sheep (0.56 ± 0.11) (Strain et al., 2002) was higher than that measured here to L3 antigens in saliva of Lleyn sheep. It should be noted however that these two heritabilities are not directly comparable as different data transformations and statistical models were used. Importantly in each case the heritability of IgA responses was approximately twice that of FEC (Bishop et al., 1996).

The strength of the relationship between salivary IgA and plasma IgA or indeed mucosal IgA at the site of infection (abomasum) remains to be determined. However, the majority of IgA present in saliva is derived from B-lymphocytes that migrate from the gut associated lymphoid tissue (Brandtzaeg, 2007a, b). This underlying biology and

**Table 2**
Estimates of phenotypic variances, heritability and phenotypic and genetic correlations between transformed IgA and production traits of UK Lleyn sheep.

| Trait | Phenotypic Variance | Heritability | Phenotypic correlation with IgA | Genetic correlation with IgA |
|---|---|---|---|---|
| transformed IgA | 0.08 (0.002) | 0.16 (0.04) | – | – |
| Faecal egg count – Strongyles (log transformed) | 2.68 (0.06) | 0.08 (0.03) | −0.002 (0.02) | −0.26 (0.02) |
| Faecal egg count – Nematodirus (log transformed) | 4.55 (0.11) | 0.15 (0.04) | 0.007 (0.02) | 0.27 (0.19) |
| Ultrasound muscle depth (mm) | 4.85 (0.09) | 0.37 (0.03) | 0.05 (0.02) | 0.08 (0.12) |
| Ultrasound fat depth (mm) | 1.04 (0.02) | 0.41 (0.03) | 0.04 (0.02) | 0.04 (0.12) |
| 21 week weight (kg) | 20.54 (0.25) | 0.45 (0.02) | 0.02 (0.02) | −0.02 (0.11) |
| ewe weight at tupping (kg) | 37.81 (0.85) | 0.37 (0.03) | 0.04 (0.04) | 0.25 (0.15) |

previous use of L3 antigens in place of L4 (McRae et al., 2014) supports our use of salivary IgA responses to L3 antigens as an indicator of the protective mucosal IgA response to L4 antigens. This rationale was upheld by the favourable genetic correlation with FEC that was observed.

There are several benefits of using salivary IgA as an indicator of resistance to *T. circumcincta*; on a practical level saliva is easy to collect for farmers or veterinarians and there is no possibility of animals not providing a sample. Samples are also easy to process in large numbers and, as salivary IgA is quite stable, can be shipped at room temperature. Alternatively the saliva (or saliva soaked swab) can be stored at −20 °C prior to analysis without impacting the result. The research reported here was conducted on Lleyn sheep, however the IgA test is appropriate for use in other breeds and so could be used throughout the sheep breeding industry as a tool to identify animals resistant to nematode infection.

Selection for resistance to nematodes based on FEC in the UK requires an average flock level of 100 eggs per gram (epg) or higher (Signet Breeding Services, 2014). For FEC it is also crucial that lambs have not been treated with anthelmintics for at least 4 weeks. IgA activity is less affected by anthelmintic use and (as with FEC) flock EBV will be useful for animals that have been exposed to similar levels of infection by grazing the same pasture. Currently the Lleyn breeders are utilising both FEC and IgA EBVs, as the required flock responses in IgA activity are still to be determined.

In this study antigen-specific responses to *T. circumcincta* larval antigens were measured. Of course the animals were grazed on pasture and so would be exposed to and infected with other parasitic nematodes (*e.g. Nematodirus battus*, *Cooperia curticei*, *Oesophagostumum* and *Trichostronglyus* species). Some cross-reactivity in the antibody response to *T. circumcincta* and these other species is anticipated and this may be beneficial to the host. However, larval culture for speciation performed on a subset of faecal samples revealed these lambs to be predominantly infected with *T. circumcincta* (unpublished). In addition to the favourable negative correlation between IgA and FEC Strongyles, a positive correlation between IgA and FEC Nematodirus was observed (Table 2). However, this correlation estimate was not significantly different from 0. The difference in direction was unexpected, given that a strong positive genetic correlation (0.61 (0.16)) between the two FEC traits was estimated. It is worth noting that Nematodirus counts are zero-inflated (Denwood et al., 2008) and so estimates using faecal egg counts for this species need to be treated cautiously.

## 5. Conclusions

Salivary IgA responses to *T. circumcincta* larval antigens can be used to identify animals resistant to nematodes for inclusion in selective breeding programs. Antigen-specific IgA responses have twice the heritability of FEC (which is currently used to identify resistant animals) suggesting that selection based on IgA would be more efficient.

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## Conflict of interest statement

We wish to confirm that there are no known conflicts of interest associated with this publication and there has been no significant financial support for this work that could have influenced its outcome. We confirm that the manuscript has been read and approved by all named authors and that there are no other persons who satisfied the criteria for authorship but are not listed. We further confirm that the order of authors listed in the manuscript has been approved by all.

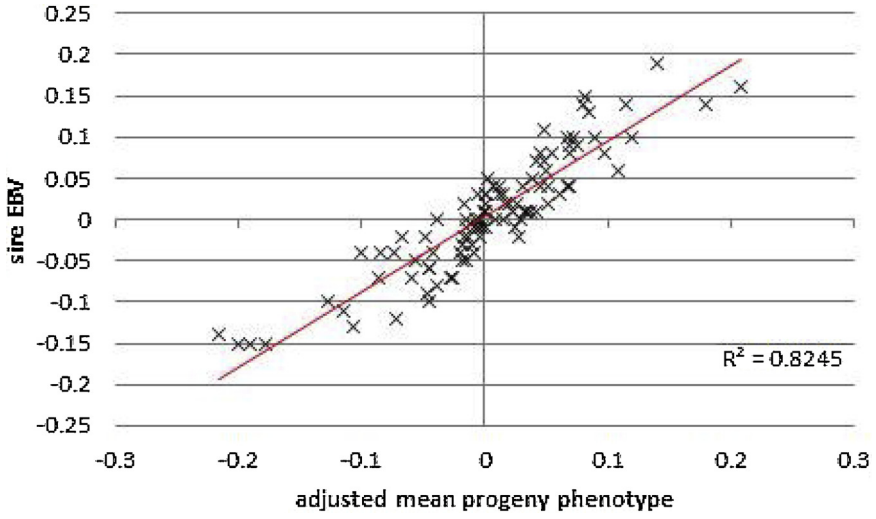


**Fig. 2.** Sire IgA EBV and the mean progeny IgA phenotype adjusted for fixed effects.

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