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RESEARCH ARTICLE

LIVESTOCK STUDIES

Identification of Candidate Genes Associated with *Eimeria* spp. Oocyst Load in Central Anatolian Merino Sheep

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Abstract

Coccidiosis caused by *Eimeria* spp. is a significant protozoal disease impacting the health and productivity of sheep and other livestock species. Host resistance to coccidiosis exhibits considerable individual variation, suggesting a genetic basis for susceptibility and resilience. This study aimed to identify genomic regions associated with oocyst load of *Eimeria* spp. in sheep using a genome-wide association study (GWAS) approach. A total of 226 sheep were phenotyped for oocyst counts using a standardized flotation technique. Genotyping was performed using a 50 K high-density SNP array. Quality control measures included filtering for minor allele frequency, call rate, and Hardy-Weinberg equilibrium. GWAS analysis was conducted using a mixed linear model accounting for relatedness among individuals. Significant associations were identified on chromosomes 1, 8 and 20. Candidate genes mapped to these regions included *PARK2*, *PACRG*, *QKI*, *PDE10A*, *RAB44*, and *CDKN1A*, which are involved in mitochondrial quality control, cellular stress response, immune modulation, and epithelial integrity maintenance. These biological functions are critical for host defence mechanisms against protozoal infections such as coccidiosis. This study reveals novel candidate genes and biological pathways potentially influencing coccidial oocyst load in sheep. These findings contribute to the understanding of host genetic resistance to Eimeria infections and may inform future breeding strategies in sheep.

Introduction

Coccidiosis, caused by protozoan parasites of the genus Eimeria, remains a major health challenge in pasture-based sheep production systems, manifesting in weight loss, diarrhea, growth retardation, and increased mortality, ultimately compromising animal welfare and farm profitability (Reeg *et al.*, 2005; Arzik *et al.*, 2022). The disease incurs both direct economic losses, such as reduced productivity and increased mortality among young animals, and indirect costs arising from medical interventions and preventive treatments. Moreover, intensive reliance on anticoccidial agents has contributed to the emergence of drug-resistant Eimeria strains, urging the need for alternative, sustainable control strategies (Karshima, 2018; Liu *et al.*, 2024).

Genetic variation among individual sheep in susceptibility to coccidiosis has been widely reported, suggesting the possibility of improving resistance through selective breeding programs (Windon, Dineen and Wagland, 1987; Gul *et al.*, 2023). Recent breeding efforts have increasingly integrated health-related traits, including parasite resistance, into selection indices to enhance herd resilience and reduce dependence on chemical treatments. Understanding the genetic basis of resistance to Eimeria infections

could thus provide critical insights for developing sustainable control strategies (Gül *et al.*, 2020; Behrem and Gül, 2022; Hayward, 2022).

The immune response to Eimeria infection involves complex interactions between innate and adaptive immunity. Physical barriers, mucosal immune defences, and the activation of antigen-presenting cells play critical roles in mounting an effective defence (McGuckin *et al.*, 2011; Chen *et al.*, 2025). Genetic factors influencing immune cell signalling, epithelial integrity, and inflammation modulation are believed to contribute substantially to individual variation in resistance (Jäger *et al.*, 2014; Sabri *et al.*, 2018; Meningher *et al.*, 2020).

Advancements in high-throughput genotyping technologies and the availability of dense genome-wide SNP panels have enabled the use of Genome-Wide Association Studies (GWAS) to dissect the genetic architecture underlying complex traits such as parasite resistance (Zhu *et al.*, 2020; Arzik *et al.*, 2025). GWAS approaches allow the identification of candidate genomic regions and biological pathways associated with disease traits, offering opportunities for marker-assisted selection (Gül *et al.*, 2016; Arzik *et al.*, 2022).

In this context, the present study aimed to uncover the genetic basis of resistance to Eimeria infections in sheep by performing GWAS on naturally infected lambs under pasture conditions. By associating oocyst burden with genome-wide SNP data, we sought to identify candidate genes and molecular pathways involved in host resistance to coccidiosis.

Materials and Methods

Study Population and Phenotyping

The study was conducted in sheep flocks located in the outskirts of Ankara province, Türkiye, characterized by a continental climate with cold winters and hot, dry summers. The region experiences an average annual rainfall of 389 mm, an average temperature of 11.7 °C, and an altitude of approximately 938 meters. The flocks grazed on semi-arid pastures with limited nutritional quality.

A total of 226 lambs from the Central Anatolian Merino (CAM) breed, including both sexes, were randomly selected from three different farms participating in the National Community-based Small Ruminant Breeding Program. All lambs shared access to the same communal pastures without supplementary feeding. Animals were born between December 2022 and February 2023, weaned at approximately three months of age, and exposed to natural Eimeria infections during the grazing season.

Fecal samples were collected directly from the rectum of each animal between six and eight months of age (August 2023). Approximately 20-30 grams of faecal material was obtained per animal, ensuring minimal contamination. Sampling was performed at least 60 days after any antiparasitic treatment. The number of Eimeria oocysts per gram (OPG) was determined using the modified McMaster technique (MAFF, 1986) and treated as a continuous trait for subsequent analyses. Blood samples were simultaneously collected from the jugular vein for genotyping purposes.

Environmental covariates such as sex, farm, birth type, and age at sampling were recorded for inclusion in the statistical models.

DNA Extraction, Genotyping, and Quality Control

Genomic DNA was extracted from whole blood samples using an automated extraction system (Qiacube HT, Qiagen Blood kit, Hilden, Germany) following the manufacturer's protocol. DNA concentration and purity were assessed using spectrophotometry (A260/280 > 1.8; A260/230 > 1.5), and samples exceeding 70 ng/µl with high integrity were selected for genotyping.

Genotyping was conducted using the OvineSNP50 BeadChip array (Illumina Inc., San Diego, CA, USA) on the iScan platform. SNP quality control was performed by excluding markers with a minor allele frequency (MAF) < 0.05, call rate < 95%, or deviation from Hardy-Weinberg equilibrium (adjusted by Bonferroni correction at $P < 0.05$/number of SNPs). Samples with a genotype call rate < 90% or excessive relatedness (Identity-by-State [IBS] > 95%) were removed from the dataset.

Statistical Analyses

Genome-wide association analyses were performed using a Mixed Linear Model (MLM) approach implemented in the GenABEL R package (Aulchenko *et al.*, 2007). The model accounted for fixed environmental effects (sex, farm, age) and genetic relatedness among individuals using a genomic relationship matrix (Astle and Balding, 2009).

The statistical model was as follows:

$$Y = \mu + X\beta + Zu + e$$

Where y represents the vector of phenotypic observations (oocyst load), µ is the overall mean, β is the vector of fixed effects and SNP effects, u denotes the vector of random additive genetic effects ($u \sim N(0,\sigma^2_u G)$), and e is the vector of random residual errors $e \sim N(0,\sigma^2_e)$. X and Z are incidence matrices relating observations to fixed and random effects, respectively.

Quantile-Quantile (QQ) plots and Genomic Control (Devlin and Roeder, 1999) were used to assess the inflation of test statistics. Bonferroni-corrected

thresholds for genome-wide and chromosome-wide significance were applied to account for multiple tests.

Functional Gene Annotation

Significant SNPs were mapped to nearby genes using the Oar_v4.0 reference genome via the NCBI Genome Data Viewer (Rangwala *et al.*, 2021). Candidate genes were annotated using DAVID Bioinformatics Resources (Huang, Sherman and Lempicki, 2009), supplemented with orthologous information from cattle, goat, mouse, and human genomes when necessary. Gene Ontology (GO) terms were used to elucidate the biological processes and pathways associated with candidate genes.

Results

The outliers in the oocyst per gram (OPG) counts for *Eimeria spp*. were detected and eliminated from the dataset, yielding a mean oocyst count of 3,115 ± 263 per gram. To achieve normality and stabilize variance, oocyst counts were subjected to log10-transformation prior to statistical analyses. Comprehensive details regarding the phenotype data are provided in Table 1. Initially, the raw genotype dataset consisted of 61,465 SNPs for 227 animals. Following quality control procedures applied to the genotypic data, 44,871 SNPs and 226 animals were retained for further analysis.

Through genome-wide association analyses, 4 significant SNPs were identified, with 2 surpassing the chromosome-wide threshold and 2 suggestive significance. The names of these SNPs and the chromosomes they are located on, along with more detailed information, are presented in Table 2.

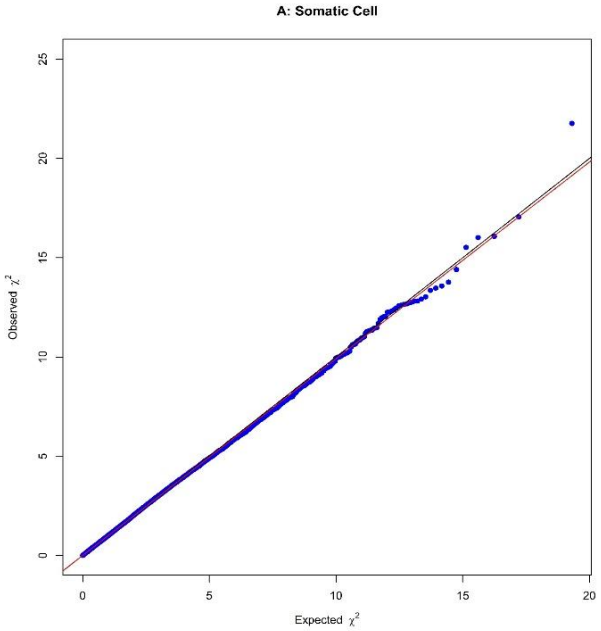

Figure 1 Quantile-quantile (Q-Q) plots of genome-wide association studies (GWAS) for the traits

Table 1. Descriptive statistics for animal age at recording (days), and fecal oocyte counts for the observations used.

Traits	N	Mean	SE Mean	Min[a]	Max[b]	SD[c]	C.V (%)[d]
Fecal oocyte count	226	3,115	263	0	28,957	3957	1,27
Age at fecal oocyte counting	227	200	2,59	124	274	39	0.19

aMin: minimum, b Max: maximum, cSD: standard deviation, dC.V: coefficient of variation.

Before the GWAS analysis, a linear mixed model was employed to assess the effects of fixed factors. Results indicated that sex, herd, and age (in days) significantly influenced log-transformed oocyst count. Consequently, these factors were incorporated into the GWAS models. Notably, herd and birth month were found to exert statistically significant effects, warranting their inclusion in subsequent analyses.

Quantile-quantile (Q-Q) plots of observed test statistics for each SNP were compared with those expected under the null hypothesis, as depicted in Supplementary Figure 1. The Q-Q plot and the estimated inflation factor lambda (λ) were obtained for the phenotype, with genomic control applied to normalize the data. Corrected p-values for each trait were derived from the GWAS, and Manhattan plots illustrating these results are provided in Figure 2.

In terms of functional annotation, based on positional information obtained from the NCBI Genome Data Viewer using the OAR_v4.0 assembly, all of these SNPs were directly associated with specific genes. Among these, several candidate genes of notable biological relevance were identified. *PARK2* (*Parkin RBR E3 Ubiquitin Protein Ligase*), involved in mitophagy and mitochondrial quality control, may contribute to cellular homeostasis under protozoan infection-induced stress. Similarly, *PACRG* (*Parkin Co-Regulated Gene*) plays a role in cytoskeletal organization and inflammatory responses, which are critical for maintaining epithelial integrity during parasite challenge.

QKI (*Quaking Homolog, KH Domain RNA Binding*), a regulator of RNA stabilization and epithelial barrier function, and *PDE10A* (*Phosphodiesterase 10A*), an enzyme controlling cAMP and cGMP intracellular

signalling pathways important for immune modulation, were also among the associated genes.

Furthermore, *RAB44* (*Member RAS Oncogene Family*) was implicated, a gene involved in vesicle trafficking and lysosomal function, which may be essential for intracellular parasite clearance. Finally, *CDKN1A* (*Cyclin-Dependent Kinase Inhibitor 1A, also known as p21*), a critical regulator of cell cycle arrest and cellular stress response, was associated with oocyst burden, suggesting a potential role in epithelial regeneration and immune defence during coccidial infection. In addition, a significant association was observed near *PCOLCE2* (*Procollagen C-Endopeptidase Enhancer 2*), a gene implicated in extracellular matrix remodelling and collagen maturation. Given the critical role of epithelial structural integrity in resistance against *Eimeria* infections, *PCOLCE2* may contribute to maintaining mucosal barrier function during the protozoan challenge. Further detailed information regarding the significant SNPs and associated genes is provided in Figure 2 and Table 2.

Experimental evidence from murine models demonstrates that Rab44 regulates granule exocytosis in mast cells and controls the release of lysosome-derived vesicles via interaction with vesicle-associated membrane protein 8 (VAMP8) (Kadowaki *et al.*, 2020). Given that *Eimeria* spp. heavily disrupt epithelial integrity and induce intracellular stress, the ability to efficiently manage lysosomal exocytosis may be critical for limiting epithelial damage and promoting the removal of infected or damaged cells. The functional localization of Rab44 to lysosomes and its role in promoting lysosomal secretion suggest that it may contribute to enhanced epithelial turnover and immune-mediated clearance during *Eimeria* infections (Noguromi *et al.*, 2023).

Moreover, recent reviews underscore the broader role of Rab44 and other Rab GTPases in immune cells, particularly in macrophages and lymphocytes, where they regulate phagocytosis, antigen presentation, and inflammatory responses (Moreno-Corona *et al.*, 2024). Notably, Rab44 expression has been associated with macrophage differentiation and cytokine production

Table 2. Significant SNPs associated with the *Eimeria* spp. fecal oocyte count.

SNP name	rs id	Chr.	Position (bp)[a]	P-value	Significance level	Associated genes	
						Name	Distance (bp)
s56894.1	rs429137901	8	84419597	$3.07x10^{-06}$	CW	*PARK2*	Within
						PACRG	~250 Kb
						QKI	~1000 Kb
OAR23_17139338.1	rs413019325	20	10643029	$3.63x10^{-05}$	*CW*	*CDKN1A*	Within
s43112.1	rs414685283	1	244063117	$6.09x10^{-05}$	*Suggestive*	*PCOLCE2*	Within
OAR6_116928489.1	rs407386965	8	87147762	$6.28x10^{-05}$	*Suggestive*	*PDE10A*	Within

[a] SNP position based on OAR_v4.0 assembly.

On chromosome 20, *RAB44* was associated with oocyst load. RAB44 plays a role in vesicle trafficking (GO:0016192) and lysosomal function (GO:0007040) (Stenmark, 2009). Efficient lysosomal degradation pathways are essential for the clearance of intracellular pathogens, implying that *RAB44* may contribute to the innate immune clearance of *Eimeria* parasites. The identification of *RAB44* as a candidate gene associated with oocyst load in *Eimeria* infections in sheep presents novel insights into the molecular mechanisms underlying host defence against protozoan parasites. Recent findings have highlighted Rab44 as an atypical member of the Rab GTPase family, characterized by its large size and additional domains such as EF-hand and coiled-coil motifs, which enable it to modulate intracellular trafficking and lysosomal Dynamics (Okuhira *et al.*, 2011).

in response to immune stimuli, implicating it as a key modulator of innate immunity. In the context of coccidiosis, where both the innate and adaptive immune responses are essential for controlling infection and minimizing pathology, Rab44-mediated vesicular trafficking and lysosomal activity could facilitate more effective antigen processing, pathogen elimination, and epithelial regeneration.

Collectively, these findings support the hypothesis that Rab44 plays a dual role in protozoan resistance: enhancing epithelial barrier protection via regulated lysosomal exocytosis and modulating immune cell functions that orchestrate the host defence against *Eimeria* spp. infections. Future functional studies specifically targeting Rab44 in ovine models will be crucial to fully elucidate its contribution to coccidiosis

resistance (Stenmark, 2009; Kadowaki *et al.*, 2020; Noguromi *et al.*, 2023; Moreno-Corona *et al.*, 2024).

PARK2 encodes an E3 ubiquitin ligase critically

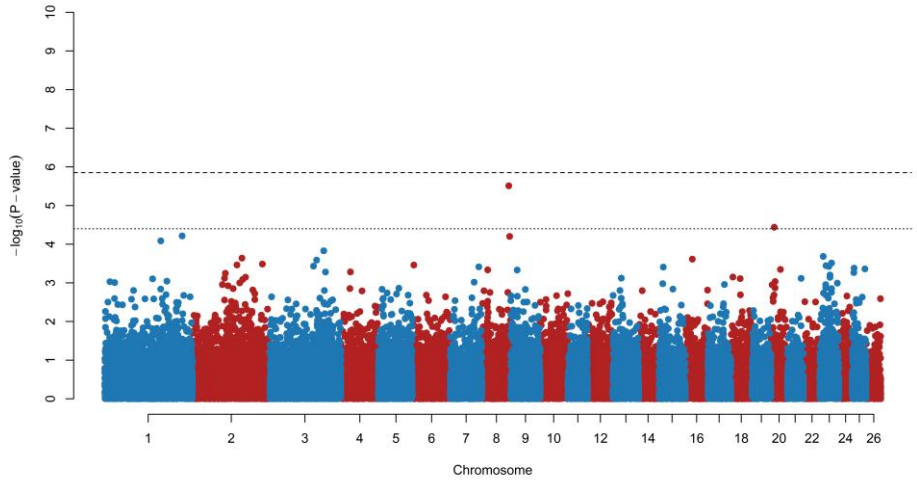

Figure 2. Manhattan plots of parasite resistance trait. The upper line indicates the genome-wide significance level, and the lower line indicates the chromosome-wide significance level. *Eimeria* spp. oocyst count at six months old.

damaged mitochondria. Protozoan infections, such as those caused by *Eimeria* spp., are known to induce cellular stress and mitochondrial dysfunction, suggesting that *PARK2* may facilitate the clearance of infected or damaged cells, thereby limiting parasite propagation and maintaining tissue homeostasis (Zilocchi *et al.*, 2020; Sun *et al.*, 2022).

Similarly, *PACRG* has been implicated in cytoskeletal organization (GO:0000226) and innate immune responses (Riva, 2024). The maintenance of intestinal epithelial barrier integrity is critical in resisting coccidial invasion, and PACRG may enhance epithelial resilience through stabilizing microtubular structures, supporting efficient repair mechanisms during *Eimeria* infection.

QKI, an RNA-binding protein that modulates mRNA stability (GO:0003723) and epithelial cell differentiation (GO:0030855), may limit the intestinal damage inflicted by *Eimeria* spp. by promoting epithelial renewal and regulating inflammatory responses (Herman and Autieri, 2017)

The identification of *PDE10A*, involved in cAMP and cGMP signalling pathways (GO:0006198; GO:0002376), underscores the importance of intracellular signalling in immune modulation. Alterations in cAMP levels can significantly affect immune cell activation and epithelial responses to infection, suggesting that PDE10A variants may modulate the host's susceptibility or resilience to coccidiosis (Koesling and Russwurm, 2015). Finally, *CDKN1A* regulates cell cycle arrest (GO:0045786) and cellular stress responses (GO:0033554) (Dutto *et al.*, 2015). During protozoan infections, the balance between epithelial cell proliferation and controlled immune activation is critical for tissue recovery, positioning *CDKN1A* as a potential modulator of epithelial regeneration during infection.

mitochondrial quality control, epithelial barrier maintenance, cellular stress responses, and immune modulation. These processes are highly relevant to the pathogenesis of coccidiosis, where epithelial disruption and inflammatory damage are hallmarks of the disease. The convergence of *PARK2*, *PACRG*, and *RAB44* in autophagy and vesicular trafficking pathways, and the involvement of *QKI*, *PDE10A*, and *CDKN1A* in inflammatory regulation, supports a multifaceted host response involving both epithelial resilience and immune defence.

Our findings are consistent with previous studies highlighting the genetic basis of resistance to gastrointestinal parasites in small ruminants (Bishop and Morris, 2007; Gül *et al.*, 2020; Arzik *et al.*, 2022), although to our knowledge, this is the first report linking these specific genomic regions and gene candidates to coccidial oocyst load in sheep.

Conclusion and Recommendations

This study performed a genome-wide association analysis to explore the genetic basis of oocyst load in sheep infected with Eimeria spp. Significant associations were identified on chromosomes 8 and 20, involving candidate genes such as *PARK2*, *PACRG*, *QKI*, *PDE10A*, *RAB44*, and *CDKN1A*. These genes are implicated in mitochondrial quality control, epithelial barrier maintenance, and immune regulation, suggesting potential mechanisms of host resistance to protozoan infections. Despite the valuable findings, the moderate sample size may have limited the ability to detect loci with small effects. Functional studies, including gene expression profiling and gene editing, are necessary to validate the roles of key genes like

PARK2, *QKI*, and *PACRG*. Furthermore, incorporating larger and genetically diverse populations, along with multi-omics approaches, would enhance our understanding of host-pathogen interactions in coccidiosis. Considering the role of humoral immunity, future research should also investigate B-cell-mediated responses. Serological assays, such as Western blot analyses using sera from naturally exposed sheep, could identify antibodies associated with resistance. These findings could support integrated breeding and vaccination strategies aimed at improving disease resilience in sheep. Overall, the study provides novel insights into the genetics of protozoan resistance and highlights opportunities for advancing selective breeding programs through functional and immunological research.

Data Availability Statement

The data presented in this study are available on a reasonable request from the corresponding author. The data are not publicly available due to the legal restriction of data deposition regarding indigenous breeds.

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Conflict of Interest

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

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