

Copyright is owned by the Author of the thesis. Permission is given for a copy to be downloaded by an individual for the purpose of research and private study only. The thesis may not be reproduced elsewhere without the permission of the Author.

**A SEARCH FOR GENETIC FACTORS INFLUENCING
IMMUNE RESPONSES TO A KILLED *MYCOBACTERIUM*
AVIUM SUBSPECIES *PARATUBERCULOSIS* VACCINE IN
AUSTRALIAN FINE-WOOL MERINO SHEEP**

Venkata Sayoji Rao Dukkipati

Thesis in fulfilment of the degree of
Doctor of Philosophy
in Animal Science



Institute of Veterinary, Animal and Biomedical Sciences
College of Sciences, Massey University
Private Bag # 11222, Palmerston North - 4442
New Zealand

2007

ABSTRACT

VSR Dukkupati (2007). A search for genetic factors influencing immune responses to *Mycobacterium avium* subspecies *paratuberculosis*. Doctoral thesis, Massey University, Palmerston North, New Zealand.

A study was conducted to identify associations between genetic markers and immune responses in Australian fine-wool Merino sheep to a killed *Mycobacterium avium* subspecies *paratuberculosis* (*Map*) vaccine (Gudair™). Blood samples and immune response data (antibody and interferon gamma, IFN- γ results) were obtained from 934 sheep from a long-term *Map* vaccination trial undertaken on three independent properties in New South Wales, Australia. Blood samples were genotyped for eight microsatellite markers that included four (DYMS1, OLADRW, OLADRB and SMHCC1) from the *Ovar-Mhc* region, two each from the SLC11A1 (OVINRA1 and OVINRA2) and IFN- γ (o(IFN) γ and OarKP6) gene regions.

Vaccination with Gudair™ induced strong antibody and IFN- γ responses as early as two weeks post-vaccination. Between-property differences in magnitude and trend of immune responses, concomitant with season of vaccination and magnitude of natural infection prevalent in individual flocks, were evident. Immune responses in controls on all the three properties remained consistently low, except for slightly elevated IFN- γ levels at a few time points in controls of properties 2 and 3, concomitant with exposure to natural infection.

There were only 2 alleles and 3 genotypes for marker o(IFN) γ but other loci exhibited extensive polymorphisms, the most occurring at OLADRW which had 42 alleles and 137 genotypes. Heterozygosities varied between 33% (OVINRA2) and 87% (SMHCC1), while polymorphic information contents ranged from 0.31 (o(IFN) γ) to 0.88 (OLADRW). Genotypes at loci DYMS1, OLADRB, SMHCC1, OVINRA1 and o(IFN) γ were in Hardy-Weinberg equilibrium (HWE), while those at OarKP6 were in HWE only when rare alleles (<1.0% frequency) were pooled with the closest size class. Departure from HWE, resulting from possible preferential amplification of alleles in heterozygotes, was evident at OLADRW and OVINRA2.

Associations between immune responses and genetic polymorphisms at the marker loci were examined by analysing both genotypic and allelic effects. The study revealed several genotypes/alleles at different marker loci to be significantly associated with antibody and IFN- γ responses to vaccination with GudairTM. However, the majority of those effects were inconsistent across the three properties. Based on significance and consistency in effects across the three properties, five genotypes (two at DYMS1 and one each at OLADRB, SMHCC1 and OVINRA1) and three alleles (one each at DYMS1, OLADRB and o(IFN) γ) were considered either 'probable' or 'most likely' to be associated with low IFN- γ responses, while a genotype at o(IFN) γ was considered 'most likely' to influence high IFN- γ responses. An allele at OarKP6 was considered 'probable' to be associated with low antibody responses to vaccination. Considering the significance of IFN- γ responses in protection against *Map*, it is likely that the identified genotype/alleles influencing IFN- γ responses to vaccination would also influence immune responses to natural *Map* infections. However, further studies need to be conducted to determine the role of these marker genotypes/alleles in protection against paratuberculosis under natural infection conditions.

Key words: paratuberculosis, OJD, Johne's disease, sheep, immune response, genetic markers, gene polymorphisms, MHC, SLC11A1, IFN- γ

ACKNOWLEDGEMENTS

I would like to place on record my heart-felt thanks to my supervisors Prof. Hugh Blair, Prof. Dorian Garrick and Assoc. Prof. Alan Murray for their invaluable guidance, inspiration and support throughout the study period. I am fortunate to undertake research under their supervision. Prof. Blair provided resources, offered direction and insightful criticism and was readily available for support at times of need. Prof. Garrick, despite being distantly away, was quite prompt, helpful and provided decisive inputs for the study, especially in statistical analyses. Assoc. Prof. Murray provided laboratory facilities to carryout genotyping and was instrumental in establishing collaboration with Australian organizations involved in Gudair™ vaccination trial.

Funding for this research was provided by Meat and Wool New Zealand and the Institute of Veterinary, Animal and Biomedical Science, Massey University. I have been supported financially by Massey University in the form of doctoral and other scholarships. Their assistance is gratefully acknowledged. Also, I would like to thank Meat and Livestock Australia, University of Sydney and the Department of Primary Industries, New South Wales for providing access to blood samples and immunological data from the Gudair™ vaccination trial.

I would like to sincerely thank Prof. Richard Whittington and Dr. Leslie Reddacliff for kindly providing blood samples and immunological data, and for their help at various stages of the study. My special thanks are due to Dr. Nicolas Lopez-Villalobos for his invaluable help and guidance in statistical analyses.

I am grateful to fellow researchers, Raechel Rigden, Dakshina Jandhyala, Satya Kannan, Kalyani Perera, Indira Rasiah, Jeremy Bryant, Kabirul Khan and Timothy Byrne for their help at various stages of my study. Also, I would like to thank Mrs. Allain Scott for academic and administrative support.

Finally and most importantly, I am very much indebted to my wife Kavitha, son Likhit and parents for their love, patience and encouragement throughout the period of research.

LIST OF CONTENTS

1. INTRODUCTION	1
2. REVIEW OF LITERATURE	5
2.1 <i>MAP</i> INFECTION IN SHEEP	5
2.1.1 Immune responses to experimental infection	6
2.1.2 Immune responses to vaccination	8
2.1.3 Genetic resistance/susceptibility to infection	10
2.2 OVINE MHC: STRUCTURE AND GENE POLYMORPHISMS	11
2.2.1 Class I genes	13
2.2.2 Class I molecules	15
2.2.3 Class II genes	16
2.2.3.1 <i>Ovar</i> -DR genes	17
2.2.3.2 <i>Ovar</i> -DQ genes	22
2.2.3.3 <i>Ovar</i> -DNA and DOB genes	26
2.2.3.4 <i>Ovar</i> -DY genes	27
2.2.3.5 <i>Ovar</i> -DM genes	28
2.2.4 Class II molecules	29
2.2.5 Class III genes	30
2.2.5.1 Complement cascade genes	31
2.2.5.2 TNF α gene	32
2.2.5.3 Other class III genes	32
2.2.6 Inheritance and polymorphism of MHC genes	33
2.2.7 Conclusion	35
2.3 OVINE MHC: ROLE IN DISEASE RESISTANCE	36
2.3.1 Association with gastrointestinal nematodiasis	36
2.3.1.1 Role of class I genes	37
2.3.1.2 Role of class II genes	39
2.3.1.3 Role of class III genes	40
2.3.1.4 Genome-wide scans	41
2.3.2 Association with bacterial diseases	41
2.3.3 Association with viral diseases	42
2.3.4 Association with other traits	43
2.3.5 Conclusion	44
2.4 OVINE SLC11A1 GENE	46
2.4.1 Structure and polymorphism	46
2.4.2 Association with disease resistance	48
2.5 OVINE IFN- γ GENE	49
2.5.1 Structure and polymorphism	49
2.5.2 Association with disease resistance	51
2.6 OTHER LOCI FOUND TO BE ASSOCIATED WITH SUSCEPTIBILITY TO TUBERCULOSIS	51
2.6.1 NOD2/CARD15	52
2.6.2 CD38	52
2.6.3 Mannan binding lectin	53
2.6.4 Vitamin D receptor	54
2.6.5 <i>sst1/Ipr1</i>	54
2.6.6 TLR2	55
2.6.7 Genes involved in type 1 cytokine cascade	55
2.7 CONCLUSION	56
3. MATERIALS AND METHODS	58
3.1 EXPERIMENTAL FLOCKS AND ANIMALS	58
3.2 VACCINATION	58
3.3 IMMUNE RESPONSES	59
3.3.1 Antibody responses	59
3.3.2 IFN- γ responses	59

(contd...)

LIST OF CONTENTS (contd...)

3.4 GENOTYPING	60
3.4.1 Blood samples	60
3.4.2 DNA extraction	60
3.4.3 Genetic markers employed	61
3.4.4 Microsatellite DNA amplification	61
3.4.5 Determining PCR product lengths and scoring genotypes	63
3.5 STATISTICAL ANALYSES	63
3.5.1 Immune responses	63
3.5.1.1 Effect of group and time	64
3.5.1.2 Correlations among immune responses	64
3.5.2 Genetic analyses	65
3.5.2.1 Estimating allelic and genotypic frequencies	65
3.5.2.2 Tests for Hardy-Weinberg equilibrium and linkage disequilibrium	65
3.5.2.3 Genetic differentiation of properties	60
3.5.2.4 Chromosome-wise haplotype analyses	66
3.5.3 Genetic effects on immune responses	66
3.5.3.1 Effect of marker genotypes on immune responses	66
3.5.3.2 Effect of marker alleles on immune responses	67
3.5.3.3 Effect of chromosome-wise haplotypes on immune responses	68
4. RESULTS AND DISCUSSION	70
4.1 IMMUNE RESPONSES	70
4.1.1 Effect of vaccination treatment (group) and time on antibody responses	70
4.1.2 Effect of vaccination treatment (group) and time on IFN-γ responses	71
4.1.3 Correlations among immune responses	73
4.1.3.1 Correlations among antibody levels	73
4.1.3.1. Correlations among IFN- γ responses	74
4.1.3.3 Correlations between antibody and IFN- γ responses	76
4.2 MARKER ALLELES, GENOTYPES AND HAPLOTYPES	78
4.2.1 Allelic and genotypic frequencies	78
4.2.1.1 Markers located in the <i>Ovar-Mhc</i> region	78
4.2.1.2 Markers located in the SLC11A1 gene	81
4.2.1.3 Markers located in the IFN- γ gene	83
4.2.2 Fit for Hardy-Weinberg equilibrium	84
4.2.2.1 Markers located in the <i>Ovar-Mhc</i> region	84
4.2.2.2 Markers located in the SLC11A1 gene	85
4.2.2.3 Markers located in the IFN- γ gene	85
4.2.3 Chromosome-wise linkage disequilibrium	86
4.2.4 Genetic differentiation of properties	86
4.2.5 Chromosome-wise haplotype frequencies	88
4.2.5.1 <i>Ovar-Mhc</i> haplotypes	88
4.2.5.2 SLC11A1 haplotypes	88
4.2.5.3 IFN- γ haplotypes	89
4.3 EFFECT OF MARKER GENOTYPES ON IMMUNE RESPONSES	90
4.3.1 Effect on antibody responses	91
4.3.1.1 DYMS1	91
4.3.1.2 OLADR B	92
4.3.1.3 OLADR W	93
4.3.1.4 SMHCC1	94
4.3.1.5 OVINRA1	95
4.3.1.6 OVINRA2	96
4.3.1.7 o(IFN)- γ	97
4.3.1.8 OarKP6	98
4.3.1.9 Power analysis	99
4.3.1.10 Summary	100

(contd...)

LIST OF CONTENTS (contd...)

4.3.2 Effect on IFN-γ responses	101
4.3.2.1 DYMS1	101
4.3.2.2 OLADRB	103
4.3.2.3 OLADRW	104
4.3.2.4 SMHCC1	106
4.3.2.5 OVINRA1	107
4.3.2.6 OVINRA2	109
4.3.2.7 o(IFN)- γ	109
4.3.2.8 OarKP6	111
4.3.2.9 Power analysis	112
4.3.2.10 Summary	113
4.4 EFFECT OF MARKER ALLELES ON IMMUNE RESPONSES	113
4.4.1 Effect on antibody responses	114
4.4.1.1 DYMS1	114
4.4.1.2 OLADRB	115
4.4.1.3 OLADRW	116
4.4.1.4 SMHCC1	117
4.4.1.5 OVINRA1	117
4.4.1.6 OVINRA2	118
4.4.1.7 o(IFN)- γ	119
4.4.1.8 OarKP6	119
4.4.1.9 Power analysis	120
4.4.1.10 Summary	121
4.4.2 Effect on IFN-γ responses	121
4.4.2.1 DYMS1	122
4.4.2.2 OLADRB	123
4.4.2.3 OLADRW	124
4.4.2.4 SMHCC1	125
4.4.2.5 OVINRA1	125
4.4.2.6 OVINRA2	126
4.4.2.7 o(IFN)- γ	127
4.4.2.8 OarKP6	127
4.4.2.9 Power analysis	128
4.4.2.10 Summary	129
4.5 EFFECT OF MARKER HAPLOTYPES ON IMMUNE RESPONSES	129
4.5.1 Effect on antibody responses	129
4.5.1.1 SLC11A1 haplotypes	129
4.5.1.2 IFN- γ haplotypes	130
4.5.2 Effect on IFN-γ responses	131
4.5.2.1 SLC11A1 haplotypes	131
4.5.2.2 IFN- γ haplotypes	132
4.5.3 Summary	133
4.6 OVERVIEW	133
5. GENERAL DISCUSSION	136
5.1 STUDY DESIGN	136
5.1.1 Inherent limitations	136
5.1.2 Employed markers and techniques	137
5.2 PHENOTYPES, MARKER ALLELES AND GENOTYPES	139
5.3 EFFECT OF MARKER GENOTYPES ON IMMUNE RESPONSES	141
5.4 EFFECT OF MARKER ALLELES ON IMMUNE RESPONSES	142
5.5 EFFECT OF MARKER HAPLOTYPES ON IMMUNE RESPONSES	143
5.6 SIGNIFICANCE OF ASSOCIATIONS	144
5.7 IMPLICATIONS AND CONCLUSIONS	147
6. LITERATURE CITED	149
7. APPENDIX	173

LIST OF TABLES

Table 1	Polymorphism of the expressed <i>Ovar</i> -DRB1 gene in various sheep breeds	21
Table 2	Polymorphism of pseudogenes <i>Ovar</i> -DRB2 and <i>Ovar</i> -DRB3 in different breeds	22
Table 3	Association of <i>Ovar</i> -Mhc genes with disease resistance	37
Table 4	Source of blood samples from control and Johne's vaccinated animals	60
Table 5	Details of markers employed in the study	62
Table 6	Correlations among antibody levels recorded at different time-points post-vaccination in vaccinates belonging to three properties	74
Table 7	Correlations among IFN- γ (Johnin-nil) levels recorded at different time-points post-vaccination in vaccinates of three properties	75
Table 8	Correlations among IFN- γ (Johnin-avian) levels recorded at different time-points post-vaccination in vaccinates of three properties	75
Table 9	Correlations between IFN- γ (Johnin-nil) and IFN- γ (Johnin-avian) levels recorded at different time-points post-vaccination in vaccinates of three properties	76
Table 10	Correlations between antibody and IFN- γ (Johnin-nil) levels recorded at different time-points post-vaccination in vaccinates of three properties	77
Table 11	Correlations between antibody and IFN- γ (Johnin-avian) levels recorded at different time-points post-vaccination in vaccinates of three properties	77
Table 12	Allelic and genotypic information pertaining to markers located in the MHC region on chromosome 20	80
Table 13	Allelic and genotypic information pertaining to markers located in the SLC11A1 gene region on chromosome 2	82
Table 14	Allelic and genotypic information pertaining to markers located in the IFNG gene region on chromosome 3	83
Table 15	Allelic and genotypic differentiation of properties and groups within properties	87
Table 16	Frequencies of OVINRA1-OVINRA2 haplotypes in three properties	89
Table 17	Frequencies of α (IFN) γ -OarKP6 haplotypes in three properties	90
Table 18	DYMS1 genotypes found to have significant effect on antibody responses to Johne's vaccination in sheep	92
Table 19	OLADRB genotypes found to have significant effect on antibody responses to Johne's vaccination in sheep	93
Table 20	OLADRW genotypes found to have significant effect on antibody responses to Johne's vaccination in sheep	94
Table 21	SMHCC1 genotypes found to have significant effect on antibody responses to Johne's vaccination in sheep	95
Table 22	OVINRA1 genotypes found to have significant effect on antibody responses to Johne's vaccination in sheep	96
Table 23	OarKP6 genotypes found to have significant effect on antibody responses to Johne's vaccination in sheep	98
Table 24	DYMS1 genotypes found to have significant effect on IFN- γ responses to Johne's vaccination in sheep	102
Table 25	OLADRB genotypes found to have significant effect on IFN- γ responses to Johne's vaccination in sheep	104

(contd...)

LIST OF TABLES (contd...)

Table 26	OLADRW genotypes found to have significant effect on IFN- γ responses to Johne's vaccination in sheep	105
Table 27	SMHCC1 genotypes found to have significant effect on IFN- γ responses to Johne's vaccination in sheep	106
Table 28	OVINRA1 genotypes found to have significant effect on IFN- γ responses to Johne's vaccination in sheep	108
Table 29	OVINRA2 genotypes found to have significant effect on IFN- γ responses to Johne's vaccination in sheep	109
Table 30	o(IFN) γ genotypes found to have significant effect on IFN- γ responses to Johne's vaccination in sheep	110
Table 31	OarKP6 genotypes found to have significant effect on IFN- γ responses to Johne's vaccination in sheep	111
Table 32	Significant effects of presence of different marker alleles on antibody responses to vaccination in sheep	114
Table 33	Significant effects of presence of different marker alleles on IFN- γ responses to vaccination in sheep	122
Table 34	Significant effects of OVINRA1 - OVINRA2 and o(IFN)- γ - OarKP6 haplotypes on antibody responses	130
Table 35	Significant effects of OVINRA1 - OVINRA2 and o(IFN)- γ - OarKP6 haplotypes on IFN- γ (Johnin-avian) responses	132
Table 36	Marker genotypes found to have significant and consistent effect on IFN- γ responses in vaccinates across three properties	142
Table 37	Marker alleles found to have significant and consistent effect on antibody and IFN- γ responses in vaccinates across three properties	143

LIST OF FIGURES

Figure 1	Schematic presentation of the structure of the <i>Ovar-Mhc</i>	13
Figure 2	Schematic presentation of the structure of MHC class I and class II molecules	15
Figure 3	Schematic presentation of the structure of the <i>Ovar-DQ</i> subregion	23
Figure 4	Trends of antibody production in response to Johne's vaccination in sheep belonging to three properties	71
Figure 5	Trends of IFN- γ (Johnin-nil) production in response to Johne's vaccination in sheep belonging to three properties	72
Figure 6	Trends of IFN- γ (Johnin-avian) production in response to Johne's vaccination in sheep belonging to three properties	72
Figure 7	Effect of DYMS1 genotypes on antibody production in response to Johne's vaccination in sheep	91
Figure 8	Effect of OLADRB genotypes on antibody production in response to Johne's vaccination in sheep	92
Figure 9	Effect of OLADRW genotypes on antibody production in response to Johne's vaccination in sheep	93
Figure 10	Effect of SMHCC1 genotypes on antibody production in response to Johne's vaccination in sheep	94
Figure 11	Effect of OVINRA1 genotypes on antibody production in response to Johne's vaccination in sheep	96
Figure 12	Effect of OVINRA2 genotypes on antibody production in response to Johne's vaccination in sheep	97
Figure 13	Effect of o(IFN) γ genotypes on antibody production in response to Johne's vaccination in sheep	97
Figure 14	Effect of OarKP6 genotypes on antibody production in response to Johne's vaccination in sheep	98
Figure 15	Sample size versus power of detecting a significant effect of genotypes at o(IFN)- γ locus on antibody responses to Johne's vaccination	99
Figure 16	Sample size versus power of detecting a significant effect of genotypes at OVINRA1 locus on antibody responses to Johne's vaccination	100
Figure 17	Effect of DYMS1 genotypes on IFN- γ (Johnin-avian) production in response to Johne's vaccination in sheep	101
Figure 18	Effect of OLADRB genotypes on IFN- γ (Johnin-avian) production in response to Johne's vaccination in sheep	103
Figure 19	Effect of OLADRW genotypes on IFN- γ (Johnin-avian) production in response to Johne's vaccination in sheep	105
Figure 20	Effect of SMHCC1 genotypes on IFN- γ (Johnin-avian) production in response to Johne's vaccination in sheep	107
Figure 21	Effect of OVINRA1 genotypes on IFN- γ (Johnin-avian) production in response to Johne's vaccination in sheep	108
Figure 22	Effect of OVINRA2 genotypes on IFN- γ (Johnin-avian) production in response to Johne's vaccination in sheep	109
Figure 23	Effect of o(IFN) γ genotypes on IFN- γ (Johnin-avian) production in response to Johne's vaccination in sheep	110
Figure 24	Effect of OarKP6 genotypes on IFN- γ (Johnin-avian) production in response to Johne's vaccination in sheep	111

(contd...)

LIST OF FIGURES (contd...)

Figure 25	Sample size versus power of detecting a significant effect of genotypes at o(IFN)- γ locus on IFN- γ responses to Johne's vaccination	112
Figure 26	Sample size versus power of detecting a significant effect of genotypes at OVINRA1 locus on IFN- γ responses to Johne's vaccination	113
Figure 27	Effect of DYMS1 alleles on antibody production in response to Johne's vaccination in sheep	115
Figure 28	Effect of OLADR B alleles on antibody production in response to Johne's vaccination in sheep	115
Figure 29	Effect of OLADR W alleles on antibody production in response to Johne's vaccination in sheep	116
Figure 30	Effect of SMHCC1 alleles on antibody production in response to Johne's vaccination in sheep	117
Figure 31	Effect of OVINRA1 alleles on antibody production in response to Johne's vaccination in sheep	118
Figure 32	Effect of OVINRA2 alleles on antibody production in response to Johne's vaccination in sheep	118
Figure 33	Effect of o(IFN)- γ alleles on antibody production in response to Johne's vaccination in sheep	119
Figure 34	Effect of OarKP6 alleles on antibody production in response to Johne's vaccination in sheep	119
Figure 35	Sample size versus power of detecting a significant effect of allele 202 at DYMS1 locus on antibody responses to Johne's vaccination	120
Figure 36	Effect of DYMS1 alleles on IFN- γ (Johnin-avian) production in response to Johne's vaccination in sheep	123
Figure 37	Effect of OLADR B alleles on IFN- γ (Johnin-avian) production in response to Johne's vaccination in sheep	123
Figure 38	Effect of OLADR W alleles on IFN- γ (Johnin-avian) production in response to Johne's vaccination in sheep	124
Figure 39	Effect of SMHCC1 alleles on IFN- γ (Johnin-avian) production in response to Johne's vaccination in sheep	125
Figure 40	Effect of OVINRA1 alleles on IFN- γ (Johnin-avian) production in response to Johne's vaccination in sheep	126
Figure 41	Effect of OVINRA2 alleles on IFN- γ (Johnin-avian) production in response to Johne's vaccination in sheep	126
Figure 42	Effect of o(IFN)- γ alleles on IFN- γ (Johnin-avian) production in response to Johne's vaccination in sheep	127
Figure 43	Effect of OarKP6 alleles on IFN- γ (Johnin-avian) production in response to Johne's vaccination in sheep	127
Figure 44	Sample size versus power of detecting a significant effect of allele 202 at DYMS1 locus on IFN- γ responses to Johne's vaccination	128
Figure 45	Effect of SLC11A1 haplotypes on antibody production in response to Johne's vaccination in sheep	130
Figure 46	Effect of IFN- γ haplotypes on antibody production in response to Johne's vaccination in sheep	131
Figure 47	Effect of SLC11A1 haplotypes on IFN- γ (Johnin-avian) responses in Johne's vaccinated sheep	132
Figure 48	Effect of IFN- γ haplotypes on IFN- γ (Johnin-avian) responses in Johne's vaccinated sheep	133

LIST OF ABBREVIATIONS

1C7	MHC classIII gene
AFO	acid-fast organism
AIC	Akaike's information criterion
AR 1	first-order auto-regressive model
Bf	B factor
BLV	bovine leukemia virus
Bota	<i>Bos taurus</i>
bp	base-pairs
C2, C4A and C4B	complement factors
CARD15	caspase recruitment domain-containing protein 15
CD	Crohn's disease
CD38	cluster of differentiation 38
CD4+	T-helper cells expressing cluster of differentiation 4
CD8+	T-helper cells expressing cluster of differentiation 8
cDNA	complementary DNA
CLIP	class II associated invariant chain peptide
CMI	cell-mediated immunity
CSIRO	Commonwealth Scientific and Industrial Research Organisation
CSR226	microsatellite in MHC class I region
CTL	cytotoxic T lymphocytes
CYP21	MHC classIII gene
DMA and DMB	genes encoding α - and β -chains of MHC class II DM molecules
DNA	deoxyribo nucleic acid
dNTP	deoxyribo nucleotide phosphate
DP, DM, DN/DO, DQ and DR	MHC class II molecules
DQA and DQB	genes encoding α - and β -chains of MHC class II DQ molecules
DRA and DRB	genes encoding α - and β -chains of MHC class II DR molecules
DRB1	ovine functional class II DRB gene
DRB2, DRB3 and DRB3	ovine non-functional DRB genes
DTH	delayed-type skin hypersensitivity
DYA and DYB	genes encoding α - and β -chains of MHC class II DY molecules
DYMS1	microsatellite in ovine DY A gene
EIA	enzyme immunoassay
ELISA	enzyme-linked immunosorbent assay
EM	expectation-maximization
ER	endoplasmic reticulum
FEC	faecal egg count
FGMT	footrot gene-marker test
G15	MHC class III gene
HIV	human immuno-deficiency virus
HLA	human leukocyte antigen
HSP70	heat-shock protein 70
HWE	Hardy-Weinberg equilibrium
IFN- γ	interferon gamma
IL	interleukin
IMF	international mapping flock
Ipr1	intracellular pathogen resistance 1
kb	kilo base-pairs
kDa	kilo Daltons

(contd...)

LIST OF ABBREVIATIONS (contd...)

LMP	low-molecular-mass protein
LRR	leucine-rich repeat
LSM	least square mean
LST1	MHC classIII gene
LT	lymphocyte transformation
LTA and LTB	MHC class III genes
<i>Map</i>	<i>Mycobacterium avium</i> subspecies <i>paratuberculosis</i>
MAS	marker-assisted selection
MBL	mannan binding lectin
MHC	major histocompatibility complex
MSMD	Mendelian susceptibility to mycobacterial disease
NK	natural killer cells
NOD2	nucleotide oligomerization binding domain 2
NRAMP1	natural resistance-associated macrophage protein 1
o(IFN)- γ	microsatellite in ovine interferon gamma gene
OD	optical density
OLA	ovine leukocyte antigen
OLADRB	microsatellite in ovine DRB2 gene
OLADRW	microsatellite in ovine DRB1 gene
<i>Ovar</i>	<i>Ovis aries</i>
OVINRA1 and OVINRA2	microsatellites in the ovine SLC11A1 gene
PBR	peptide binding region
PCR	polymerase chain reaction
PPD	purified protein derivative
PSO	polymorphism-specific oligonucleotide
PTB	paratuberculosis
QTL	quantitative trait loci
RFLP	restriction fragment length polymorphism
RSCA	reference-strand-mediated conformation analysis
RT-PCR	reverse transcription polymerase chain reaction
SDS-PAGE	sodium dodecyl sulfate - polyacrylamide gel electrophoresis
SE	standard error
Sh-LA	sheep leukocyte antigen
SLC11A1	solute carrier family 11 member 1
SMHCC1	microsatellite in MHC class I region
SNP	single nucleotide polymorphisms
SSCP	single strand conformational polymorphism
sst1	susceptibility for tuberculosis 1
STR	simple tandem repeat
TAP	transporter-associated protein
TAPBP	transporter-associated protein binding protein
T-cells	thymus-derived lymphocytes
TCR	T-cell receptor
Th1	T-helper cells subset 1
Th2	T-helper cells subset 2
TLR	toll like receptor
TNF	tissue necrosis factor
VDR	vitamin D receptor