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# Explaining and exploiting MHC diversity.

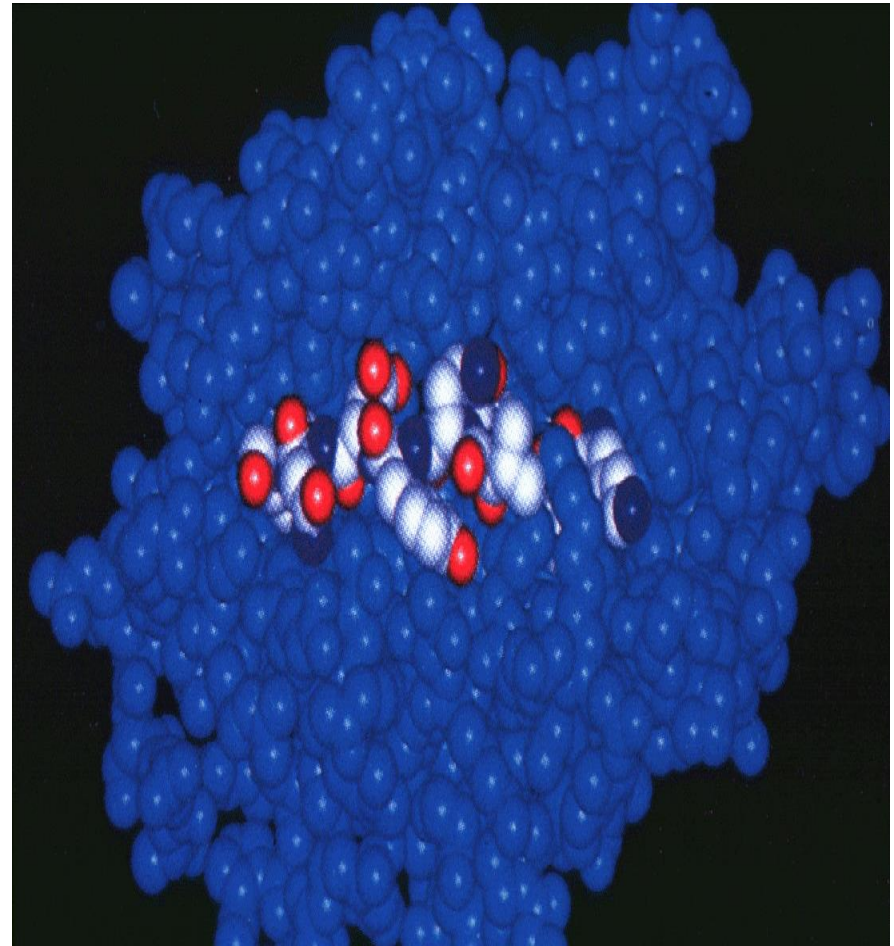
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# Major Histocompatibility Complex

- MHC most important for disease resistance
- MHC most diverse region
- MHC presents antigen
- Unsure how selective forces maintain MHC diversity



# Aim:

## To understand MHC diversity

- Objectives:
  - Nematodes as a model system
  - MHC association with resistance
  - Mechanisms maintaining MHC diversity
  - MHC in selective breeding

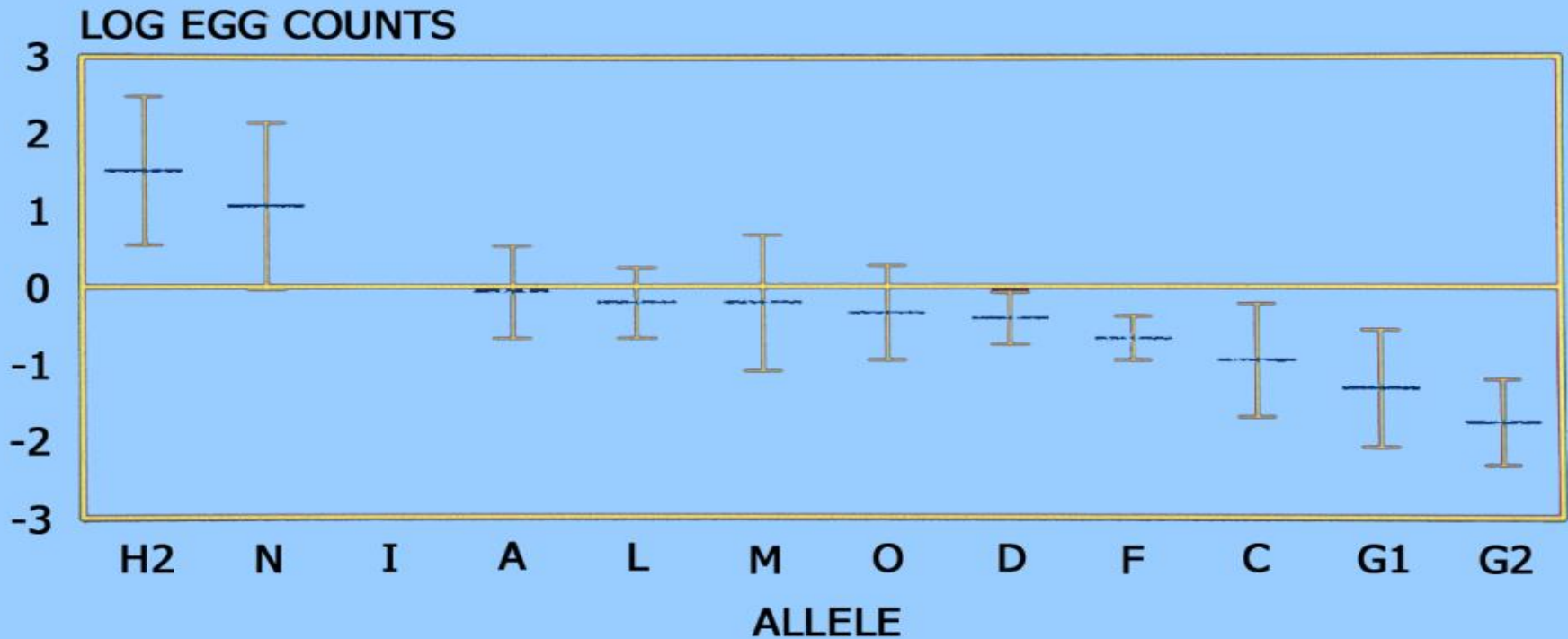
# Nematodes as a model

- Natural history
- Quantitative genetics
- Immune mechanisms
- Importance of MHC
  - GWAS, candidate gene

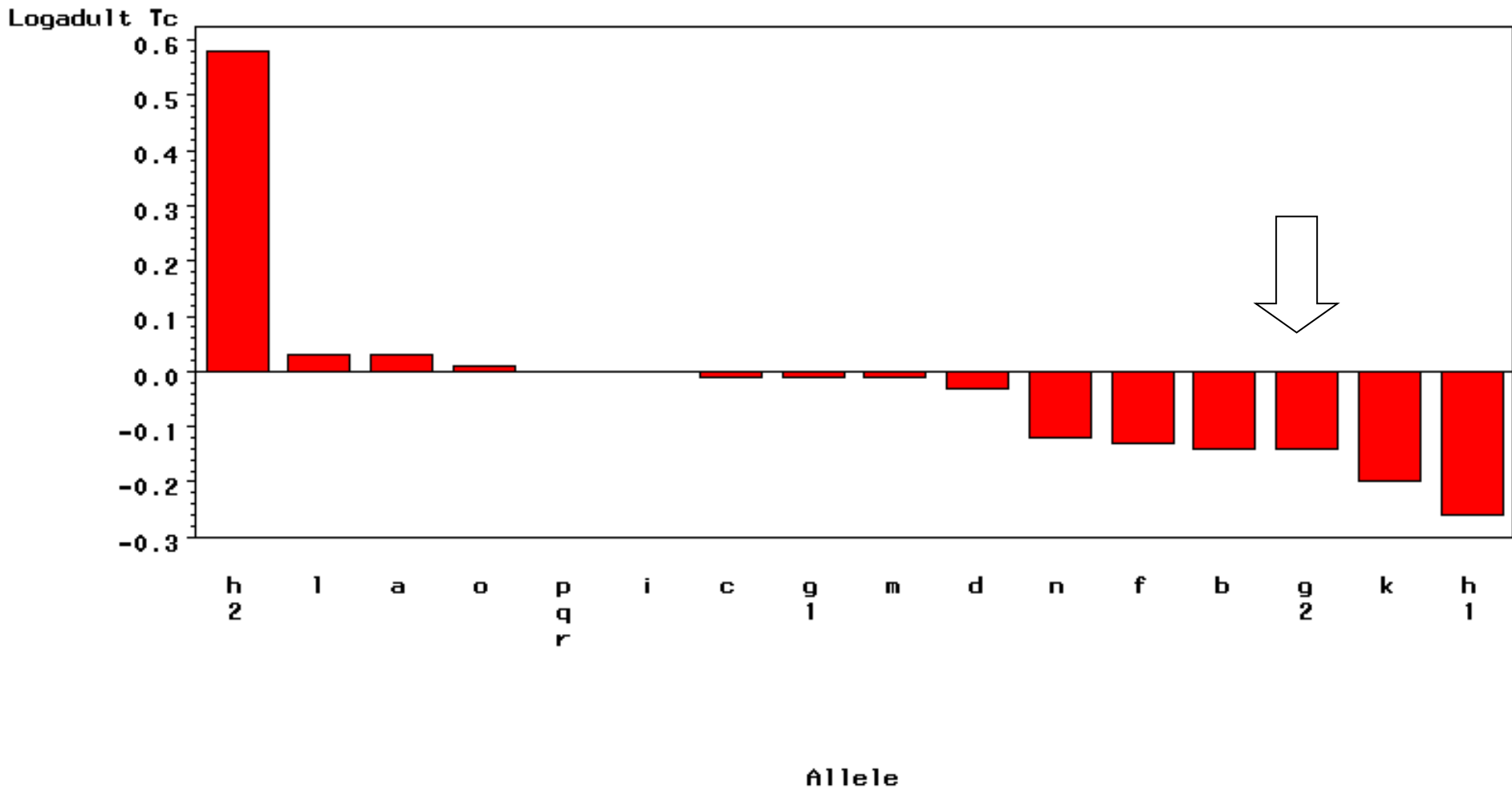
# MHC and nematodes

- Mice, cattle, sheep, pigs, fish
- Sheep
  - Scotland, Ireland, Poland, Spain
- Allele G2 (1101) association in Blackface and Suffolk

# DRB1 alleles associated with FEC

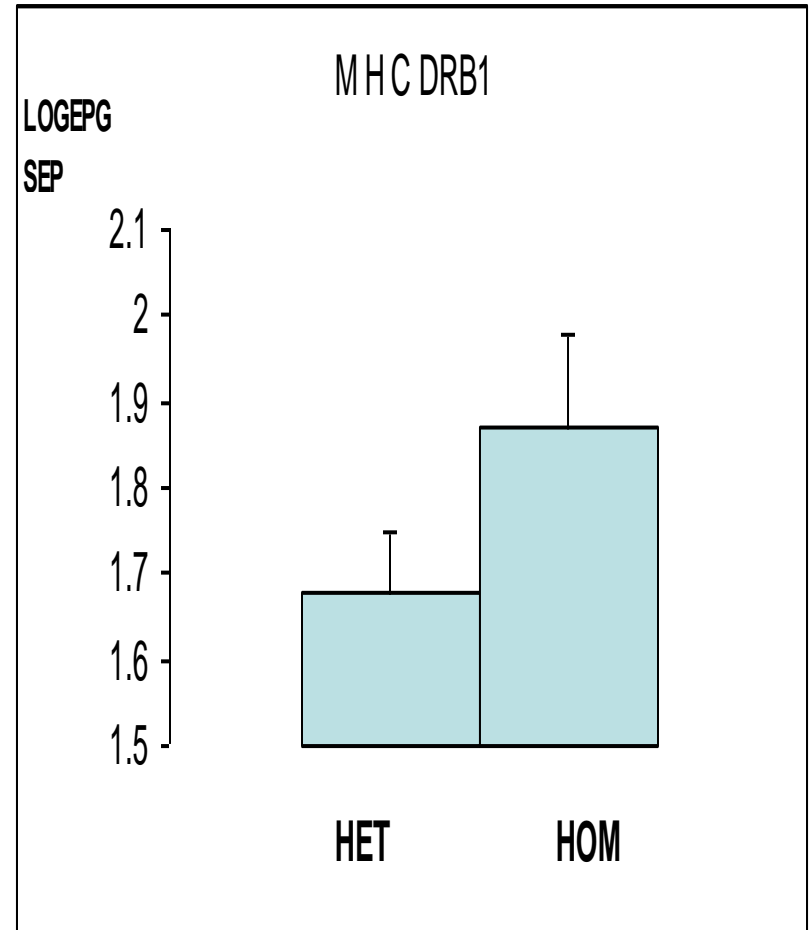


# MHC associated with worm number



# Heterozygote advantage

- Heterozygotes lower epg
- Heterozygotes recognise more parasite molecules





# Texel

- More resistant to nematodes than Suffolk
- Allele 1101 present
- No MHC association



# Sheep MHC Class II region Antigen presenting genes

*DRA DRB1 DQA1 DQB1 DQA2 DQB2*

# MHC Structure in Texel flock

- Many alleles
  - *DRB1* 18, *DQA1* 9, *DQB1* 13, *DQA2* 8, *DQB2* 16
- Few Haplotypes
  - 21 / 269,568
- Copy number variation in DQ
  - 1-3 loci per haplotype

# Texel DRB1 alleles

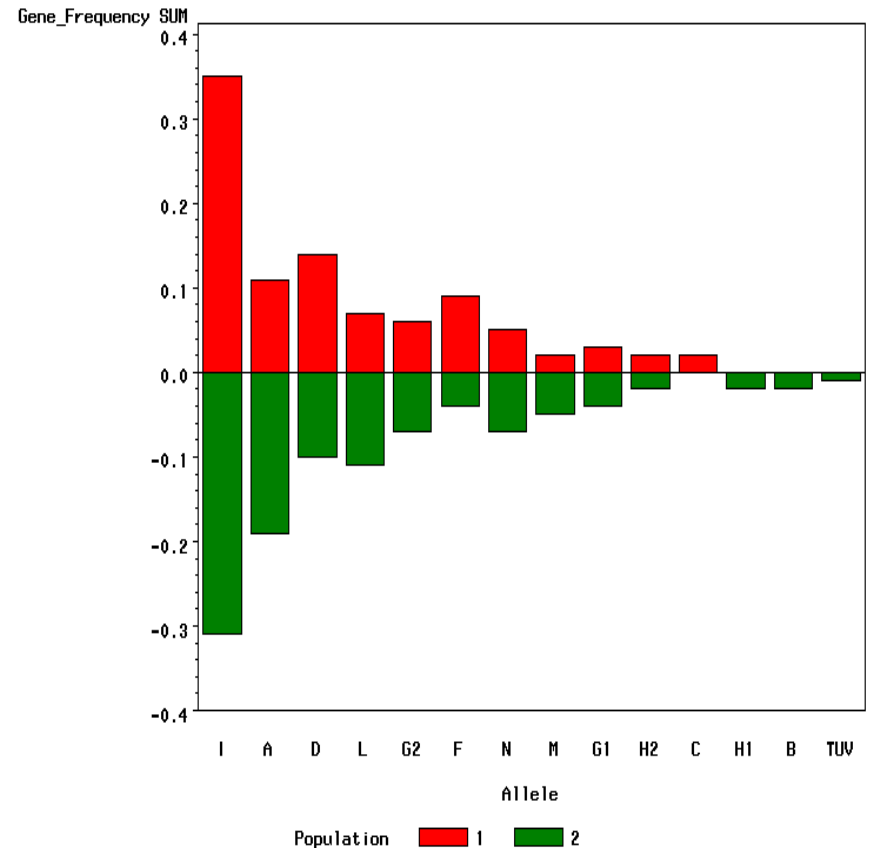
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0201 HFLEYSTSECHFFNGTERVRFLDRYFYNGEETLRFDSDWGEYRAVAELGRPDAKYWNSQKDFLEQTRAAVDTYCRHNYGVI ESFSVQRR 00
1101 .....EI..RK.....G.....00
2202 .....HK.....YV.....RK..N.....G...T...00
0801 .....AK..R.....E.....YV.....RS.E.....RK..N.....G...T...00
2002 .....AK..R.....E.....YV.....RK..N.....F.....00
1001 .....YV.....EI..RR..TE.....00
1202 .....HK.....YV.....F.....E.....EI..RR..TE.....00
0302 .....TKK..R.S.....YV.....EI..RR..TE.....00
1501 .....YV.....QS.EH.....EL..RR..E.....00
1801 .....TKK..R.....Y.....YV..N.....EL..RK..N.....G...T...00
FM000807 .....TKK..R.S.....YA.....RS.E.....EI..RK.....G...T...00
0805 .....HK.....H.....FV.....F.....RS.E.....EL..RR..TE.....G...T...00
0102 .....TKK..R.S.....H.....RA.....G.....00
0401 .....HK..R.S.....Y.....YV..N.....E.....00
HG3616641 .....HK..R.S.....Y.....H.....YV..N.....RS.E.....E.....00
0701 .....TKK.....L.E.....YV.....F.....SR.T.....G...T...00
1401 .....TKK.....L.E.....YV.....F.....QS.E.....EI..SR.T.....00
0901 .....YR.....L.E..H...FA.....F..T...A.EQ...NI...K..E.N.V.....F..A...00

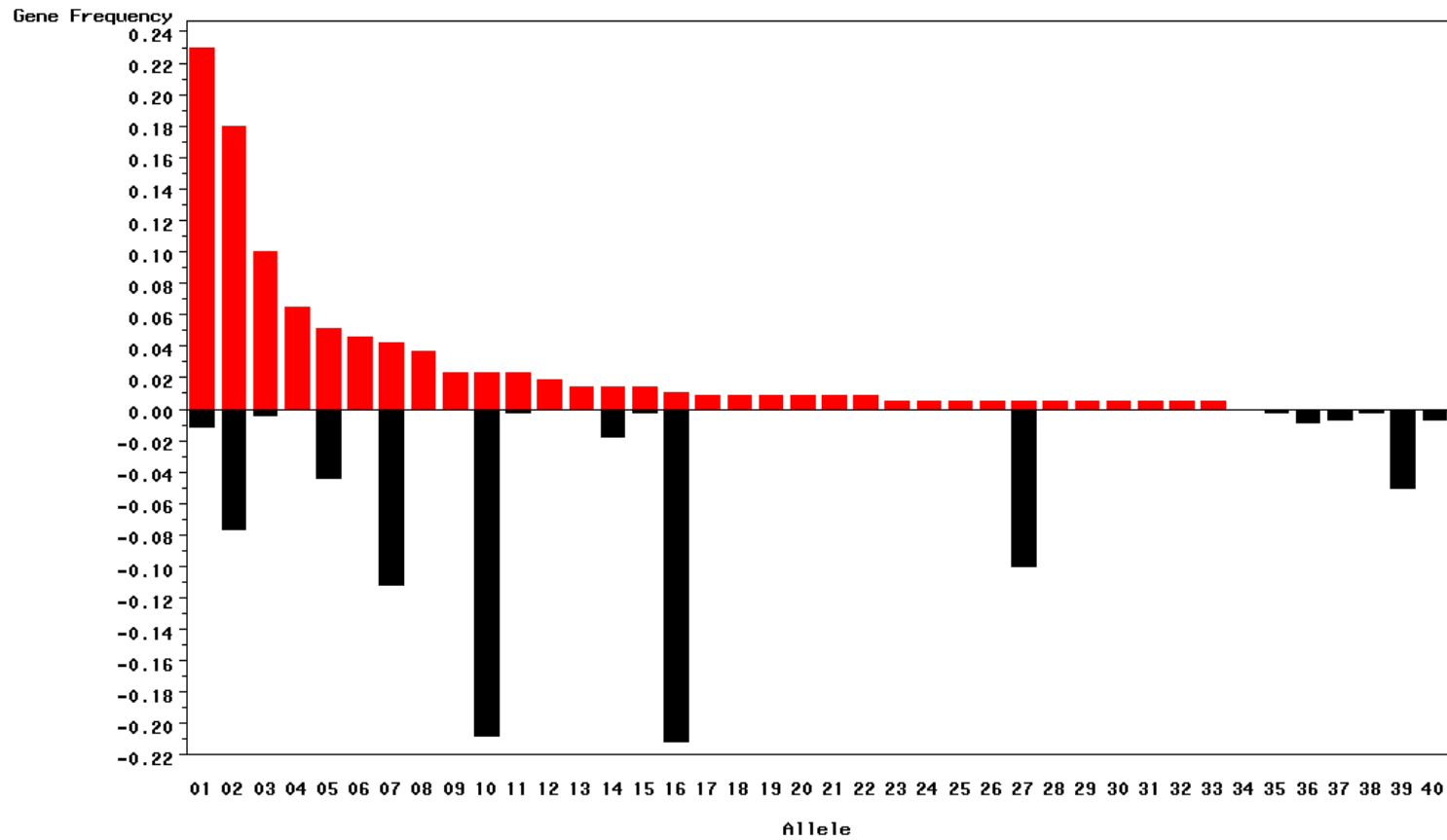
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# Differences among flocks of the same breed

- Two Blackface flocks
- Differ in alleles present
- Differ in frequency



# MHC-DRB1 frequencies in Scottish Blackface and Texel sheep



# Fine mapping

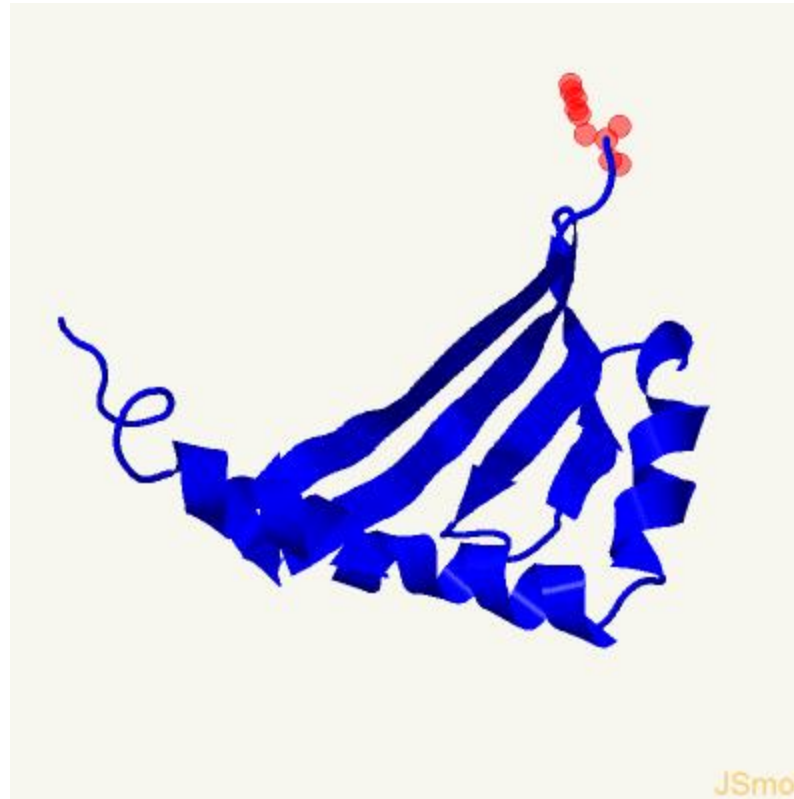
- DRB1 DQA1 DQB1 DQA2 DQB2
- SB G1 CC55881 \*0901 GU191460 New5
- Texel GSF CC55881 \*0901 GU191460 New5

# Fine Mapping 2

- DRB1 DQA1 DQB1 DQA2 DQB2  
  
SB 1101 AY312394 Null \*0101 AJ238946  
  
Texel 1101 AY312392 Null \*0101 AJ238946  
Texel 1101 AY312392 Null \*0101 AJ238935



# Sheep DRB1 structure



# MHC and nematode resistance

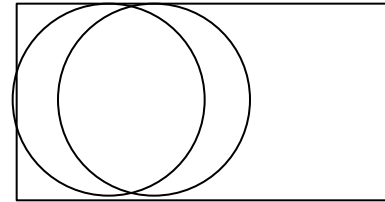
- Influences IgE mediated worm number
- Allele differences
- More than one locus
- Heterozygote advantage

# Selection and MHC diversity

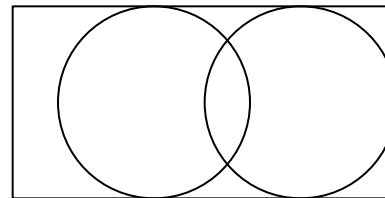
- Balancing selection
  - Frequency-dependent selection
  - Variation across time and space
  - Heterozygote advantage

# Heterozygote advantage

- Symmetric overdominance X



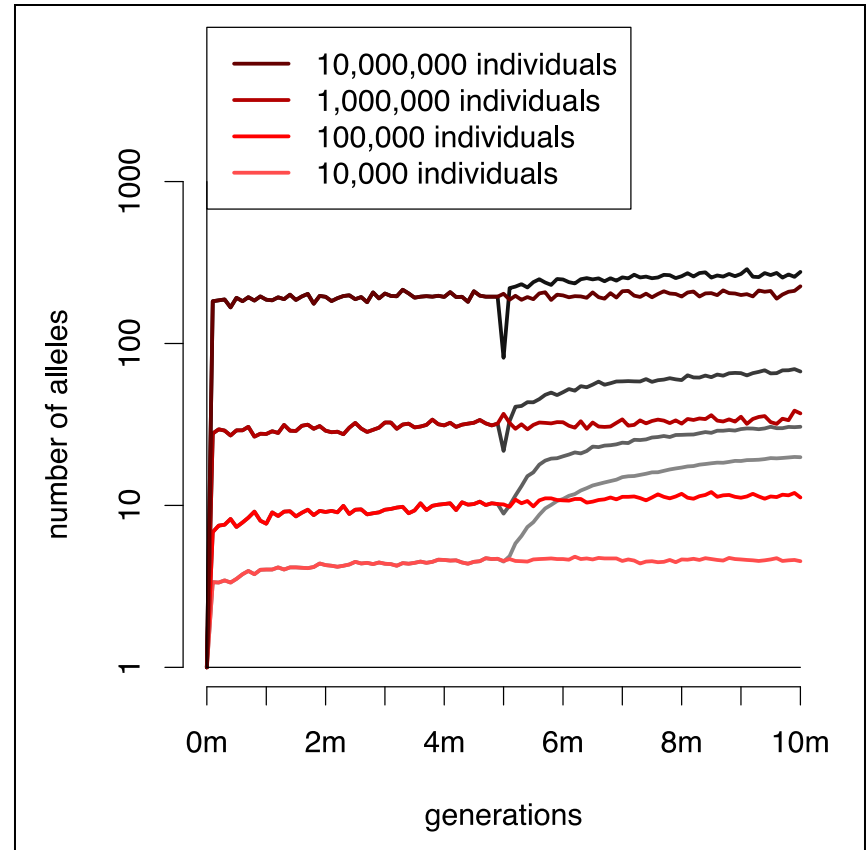
- Asymmetric overdominance X



- Divergent allele advantage ?

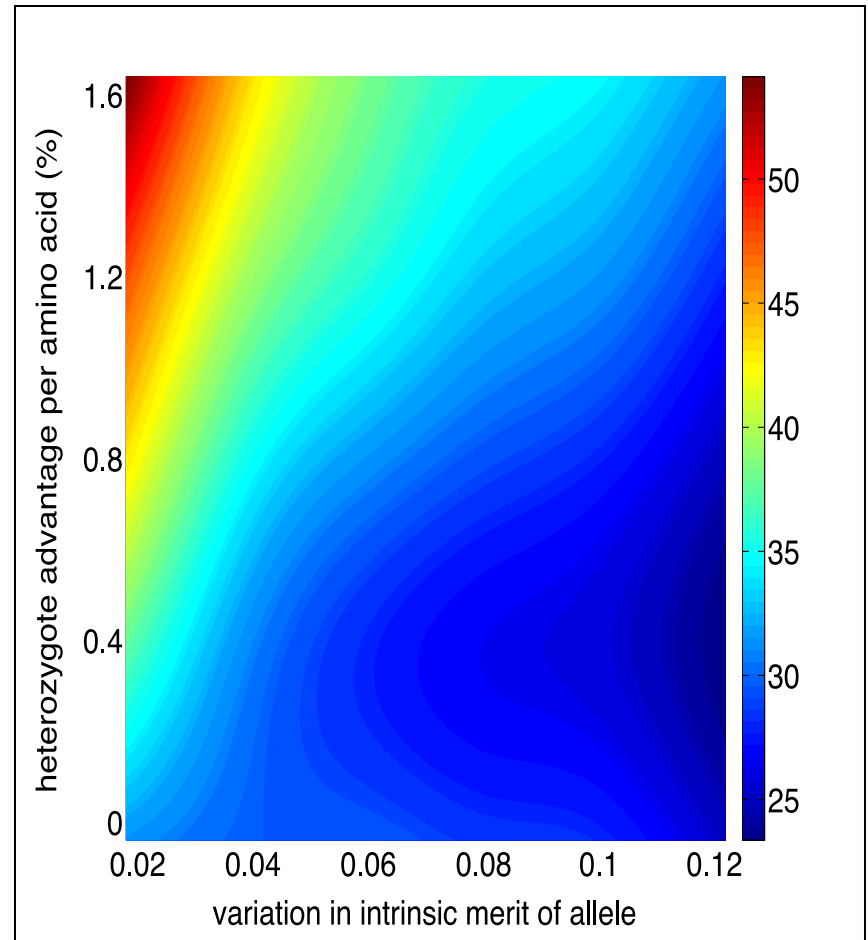
# Evolution of MHC diversity

- Start with single allele
- Diversity and population size
- Subpopulations increase diversity

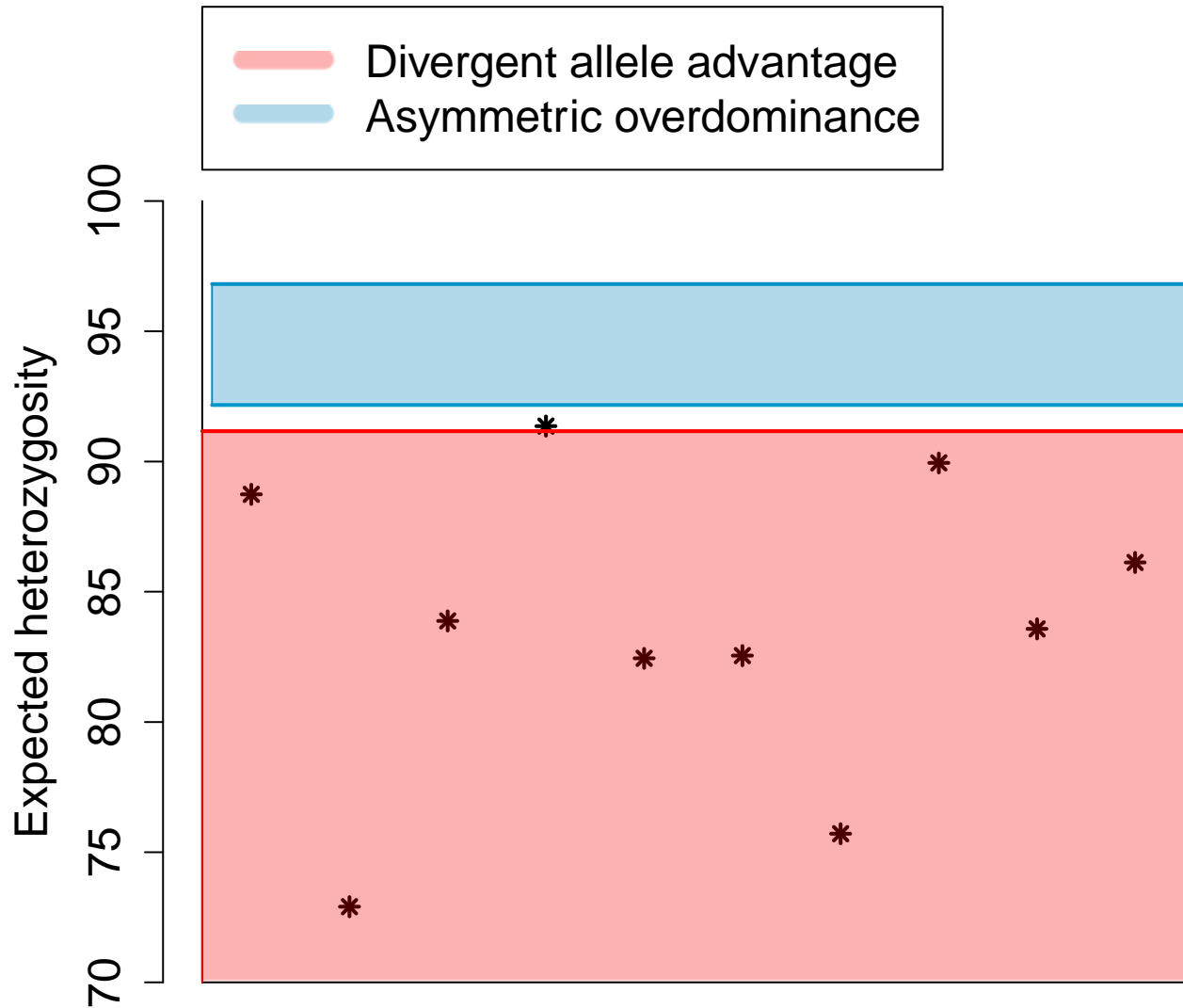


# Selective forces and number of alleles

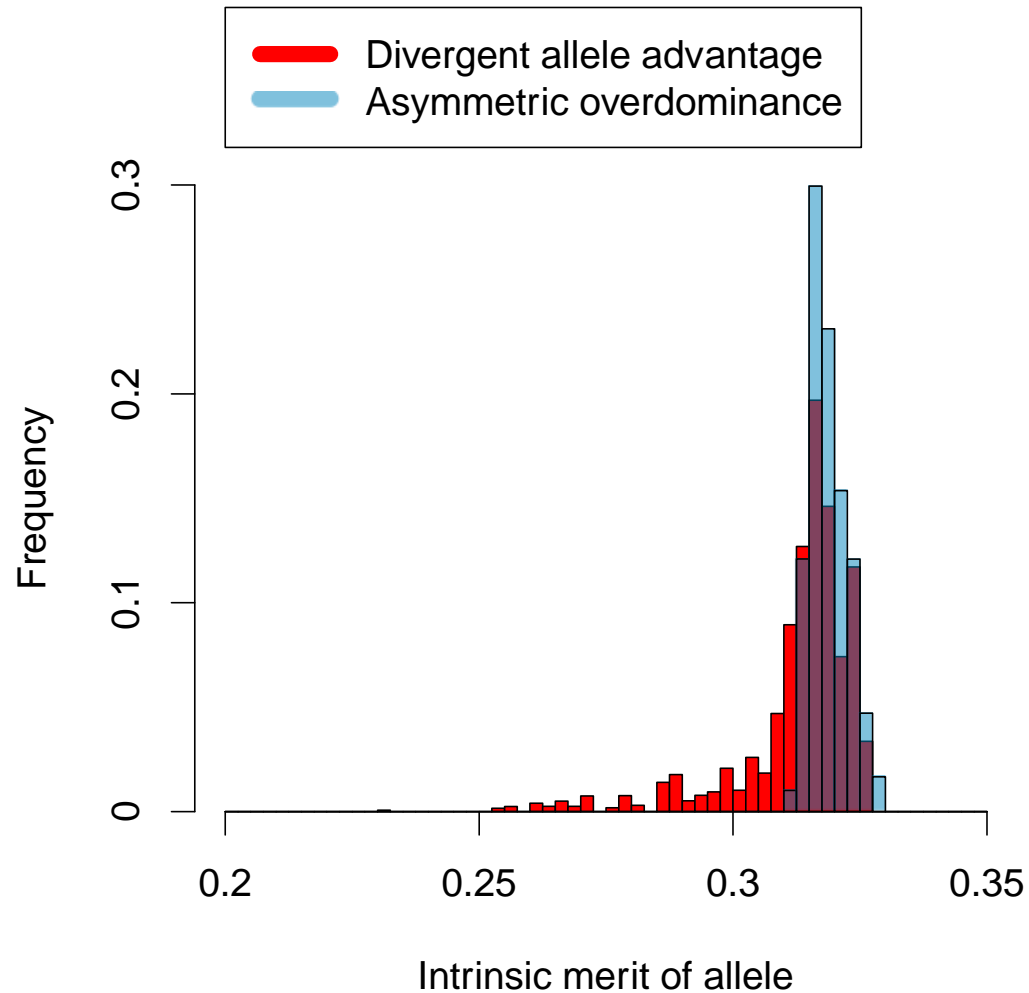
- For many alleles
  - High heterozygote advantage
  - Low variation among alleles



# Expected Heterozygosity in 10 ruminant populations

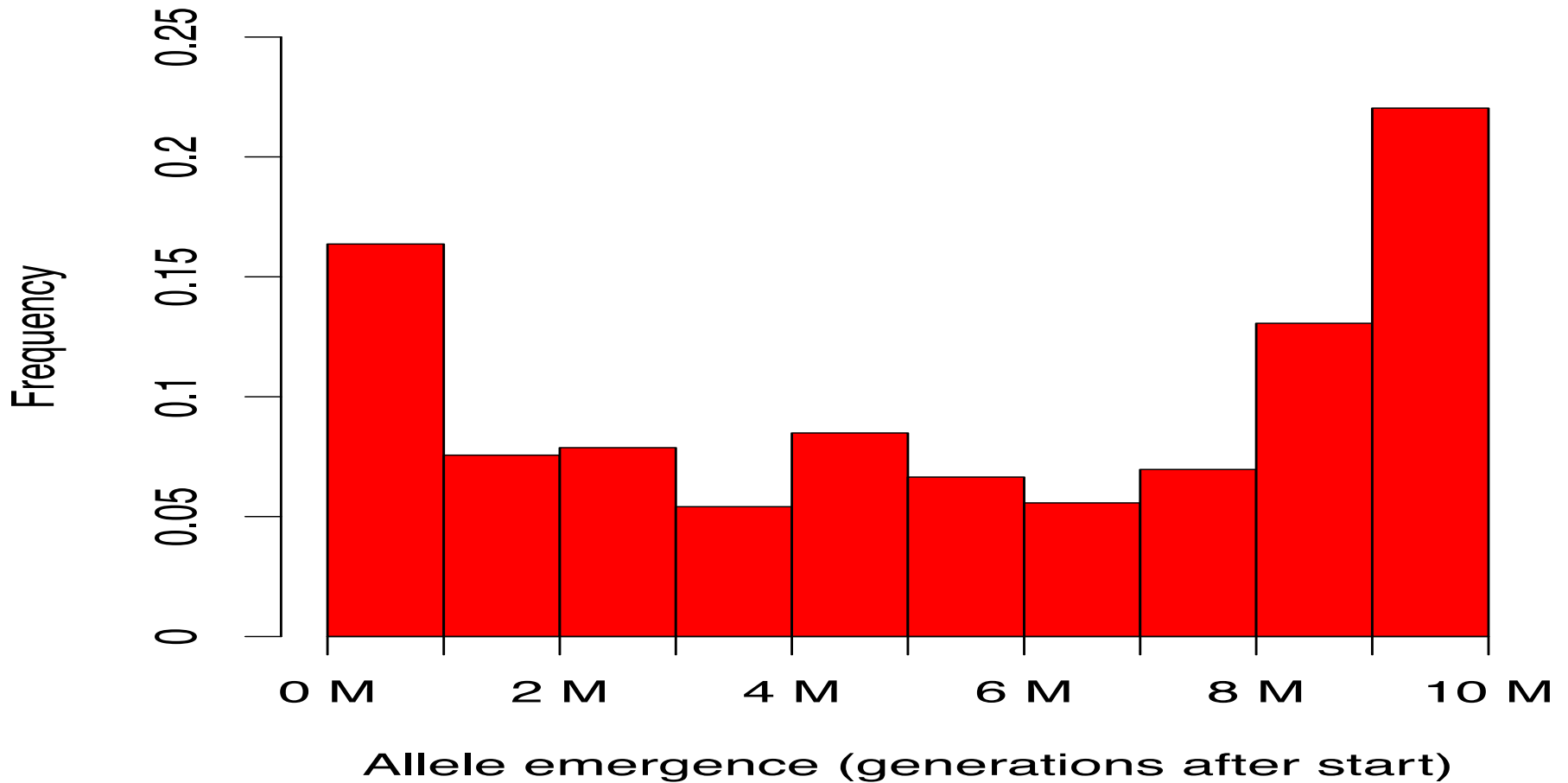


# Variation among alleles in fitness





# Age of alleles under DAA



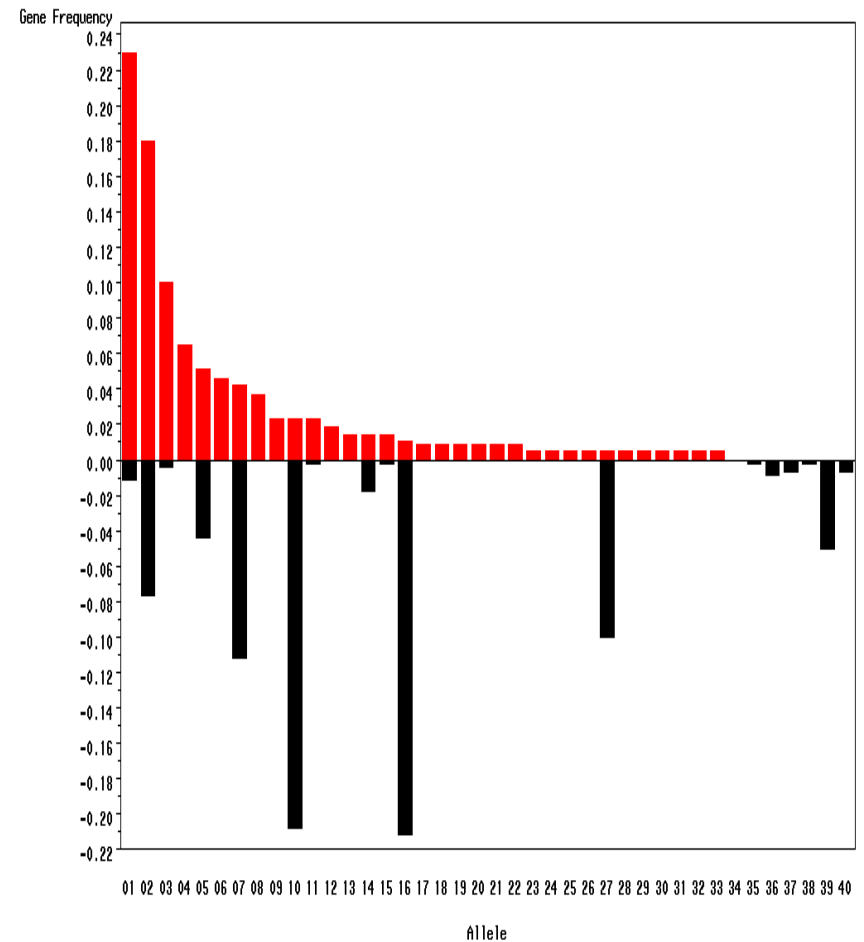
# Genomic selection

- Large reference population
- Identify SNP associated with desired trait
- Sum SNP



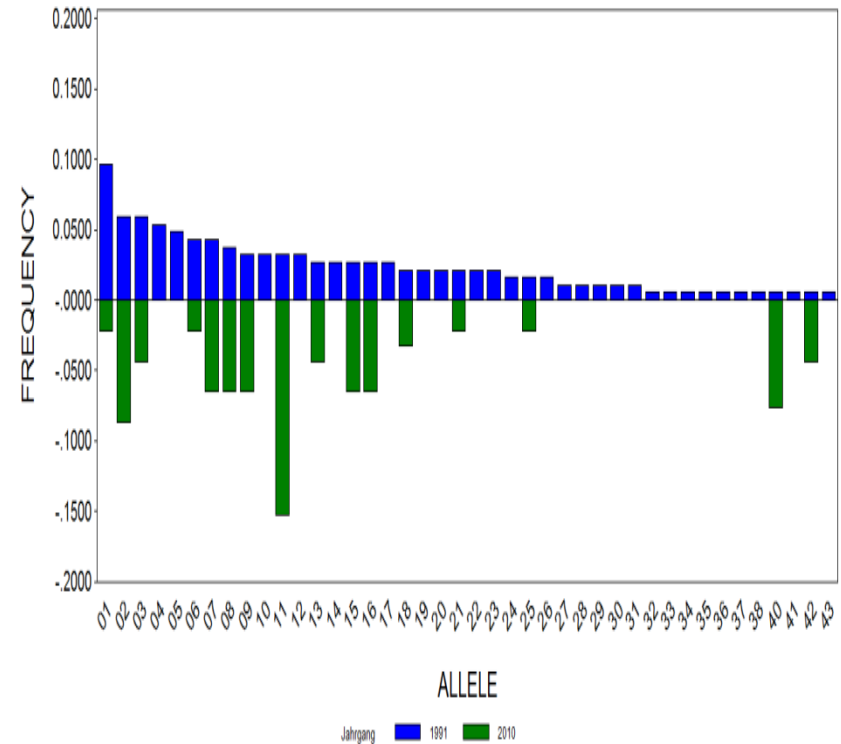
# Using MHC by mimicking NS

- Define haplotype
- Weight haplotype by frequency
- Weight haplotype by diversity and phenotypic effect



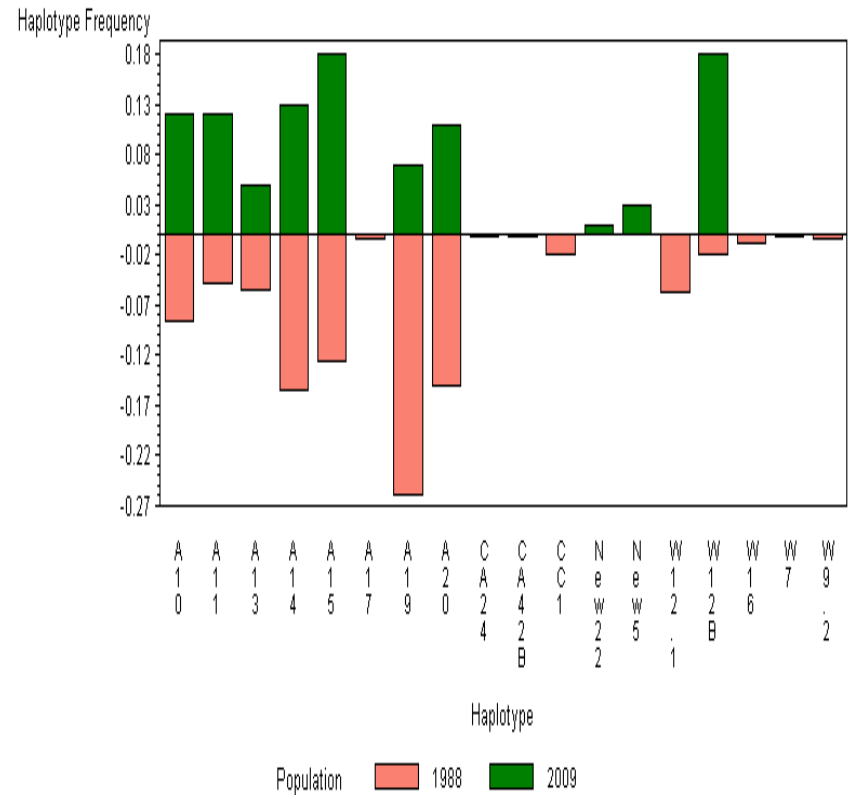
# DQB2 Frequencies following selection for nematode resistance

- Allele frequencies change
  - Drift and selection
- Heterozygote advantage
- High diversity after selection



# MHC in Canadian Bulls

- Canadian Bulls tested
  - No loss of diversity
  - Changes too great for drift
  - Heterozygote advantage



# Future work

- Selective breeding
- Response to vaccination
  - Vaccine design
  - Selection criterion

# Summary

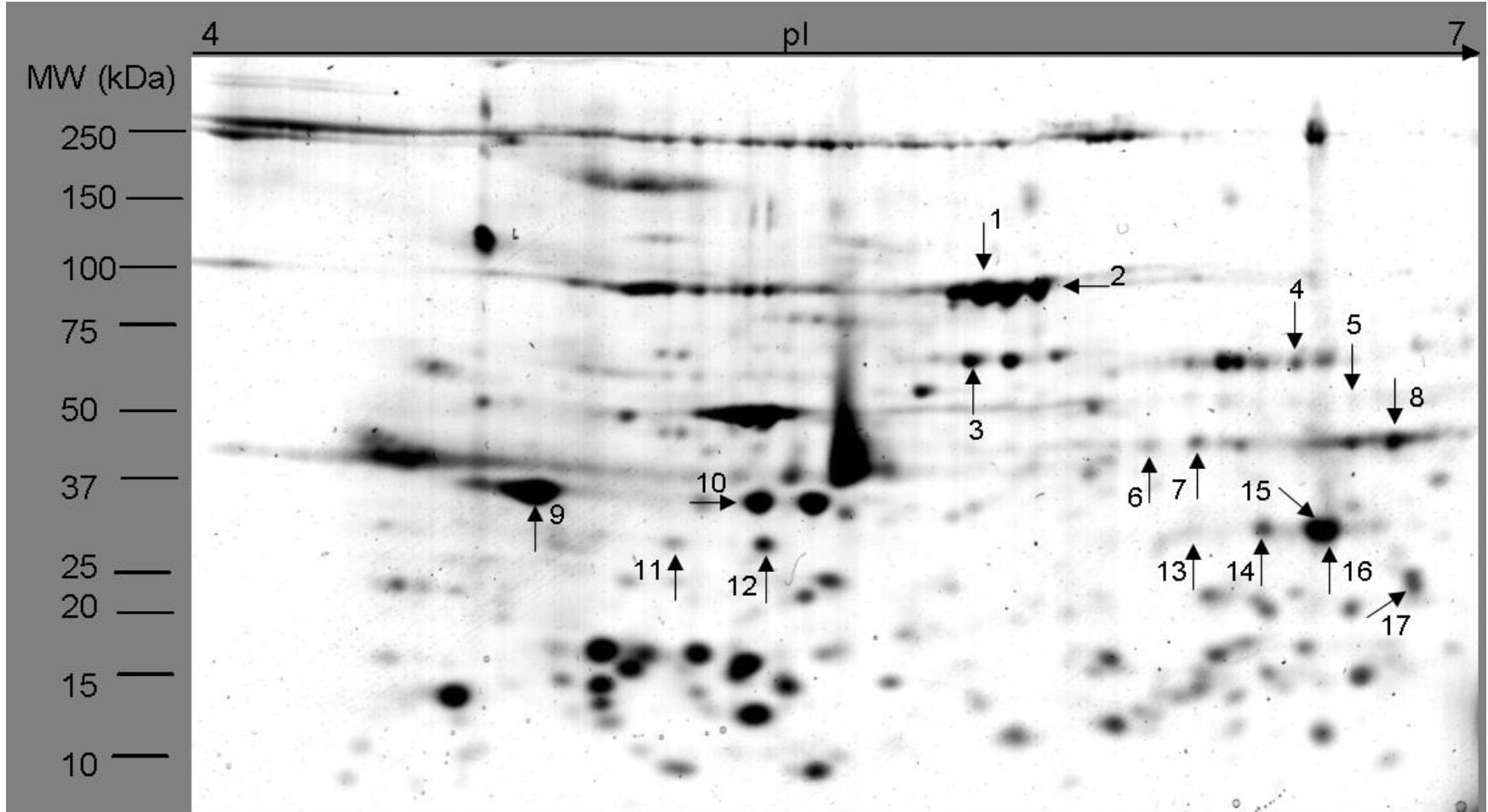
- Ovine MHC very diverse but few haplotypes
- MHC associated with reduced parasite numbers
- DAA primary driver of MHC diversity
- Use MHC in selective breeding

# Acknowledgements

- K. Fairlie-Clarke, A. Ali, N.M.M Isa, A. Stear, C. McComb, G. Nikbakht
- Thorsten Stefan, Louise Matthews



# Identification of IgE targets on L3

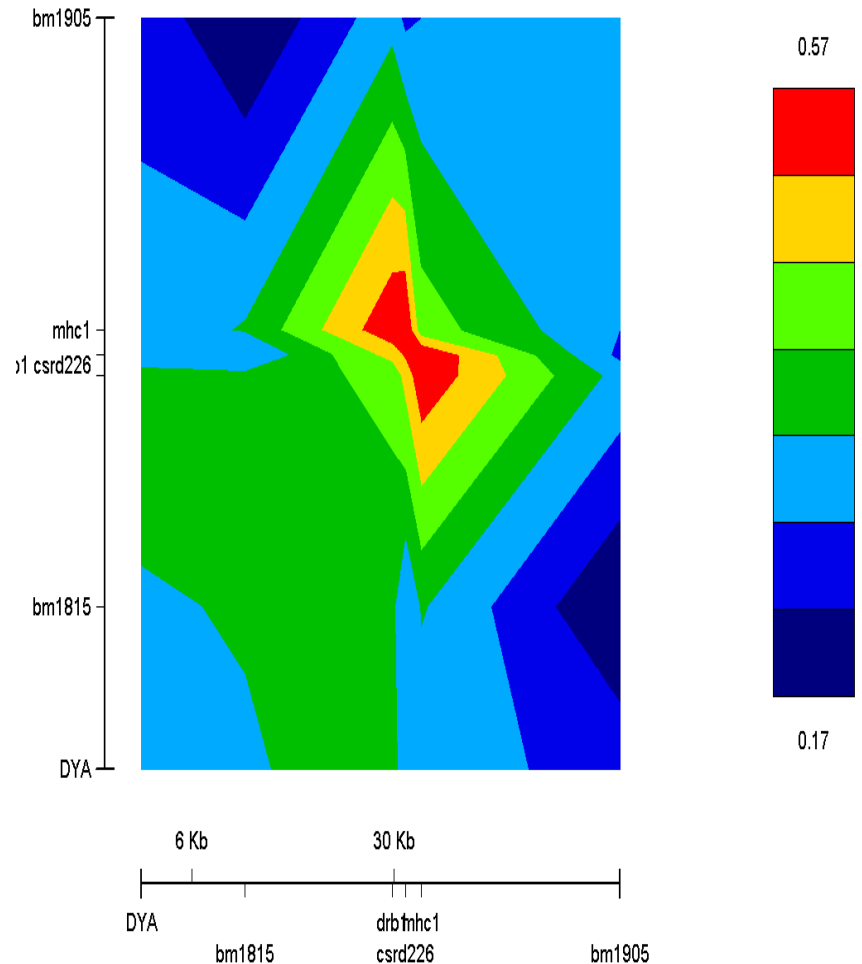


# Allergens from *T.circumcincta*

<b>Spot</b>	<b>Protein</b>	<b>pI</b>	<b>MW</b>
<b>1,2</b>	<b>Paramyosin</b>	<b>5.4</b>	<b>100878</b>
<b>3</b>	<b>HSP70</b>	<b>5.4</b>	<b>69838</b>
<b>4</b>	<b>Intermediate filament protein B</b>	<b>5.73</b>	<b>67767</b>
<b>5</b>	<b>Propionyl coenzyme A carboxylase</b>	<b>6.15</b>	<b>58707</b>
<b>6,7,8</b>	<b>Putative calponin like protein</b>	<b>5.33</b>	<b>44196</b>
<b>9</b>	<b>Tropomyosin</b>	<b>4.64</b>	<b>33031</b>
<b>10</b>	<b>Disorganised muscle family member</b>	<b>4.98</b>	<b>35750</b>
<b>11,12,13,14,15,16</b>	<b>Galectin</b>	<b>6.07</b>	<b>31711</b>
<b>17</b>	<b>Prohibin-like molecule</b>	<b>6.01</b>	<b>30083</b>

# High LD in ovine MHC

- Class II 160,000 bp
- Population structure
- Difficult to identify causative mutation



# Texel Class II Haplotypes

	DRB1	DQA1	DQB1	DQA2	DQA2-like	DQB2	Freq
1	0901	Z28518	LN868261	AY312388	NULL	AJ238939	0.0660
2	0601	M33304	NULL	AY312377	NULL	AJ238935+ AH001247	0.0340
3	0401	Z28418	Z28423	AY312381	NULL	HQ728669	0.0106
4	1601	AF276956	LN868260	AY312381	NULL	GU191456	0.1255
5	1501	AY265308	U07032	AY312386	NULL	LN811403	0.0085
6	1202	LN827890	HM367630	AY312387	NULL	GU191453	0.0064
7	0201	M33304	GU191455	AY312375	AY312392	GU191459+ U07033	0.0128
8	0805	Z28518	Z28424+ GU191455	AY312382	NULL	GU191459	0.0021
9	2202	LN736359	LN868258	AY312389	NULL	AJ238945	0.0128
10	2202	M33304	LN868258	AY312377	NULL	ABV90470	0.0043
11a	1101	NULL	NULL	AY312375	AY312392	AJ238935	0.1489
11b	1101	NULL	NULL	AY312375	AY312392	AJ238946	0.0532
12	1401	LN827890	HM367631	AY312387	NULL	GU191460	0.0787
13	0102	M33304	LN868259	AY312377	NULL	ABV90470	0.1298
14	HQ515541	M33304	LN868264	AY312377	NULL	AH001247	0.0106
15	0302	LN736359	LN868258	AY312389	NULL	AJ238945	0.0404
16	1001	M33304	GU191455	AY312382	NULL	GU191459	0.2106
17	0701	NULL	AJ238943	AY312375	AY312392	LN811404	0.0128
18	2002	M33304	LN868259	AY312377	NULL	ABV90470	0.0213
19	FM998807	M33304	LN868259	AY312377	NULL	ABV90470	0.0085
20	1001	LN827890	AJ238934	AY312387	NULL	GU191457	0.0021

# Variation among alleles in fitness (2)

