Genome-wide associations of immune-associated traits in dairy cows

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Introduction

SRUC

- **Low-cost** ... yping technology

...2010)

Introduction

Inclusion of **immune response**
phenotypes in selection indices may be a **viable option**
to **decrease disease** and **improve** animal **health**

(Abdel-Azim *et al.,* 2005; Thompson-Crispi *et al.,* 2012a; Mallard *et al.,* 2015)

heritability c^2 repeatability

0.8
0.7
0.6
0.5
0.4
0.3
0.2
0.1
0.0

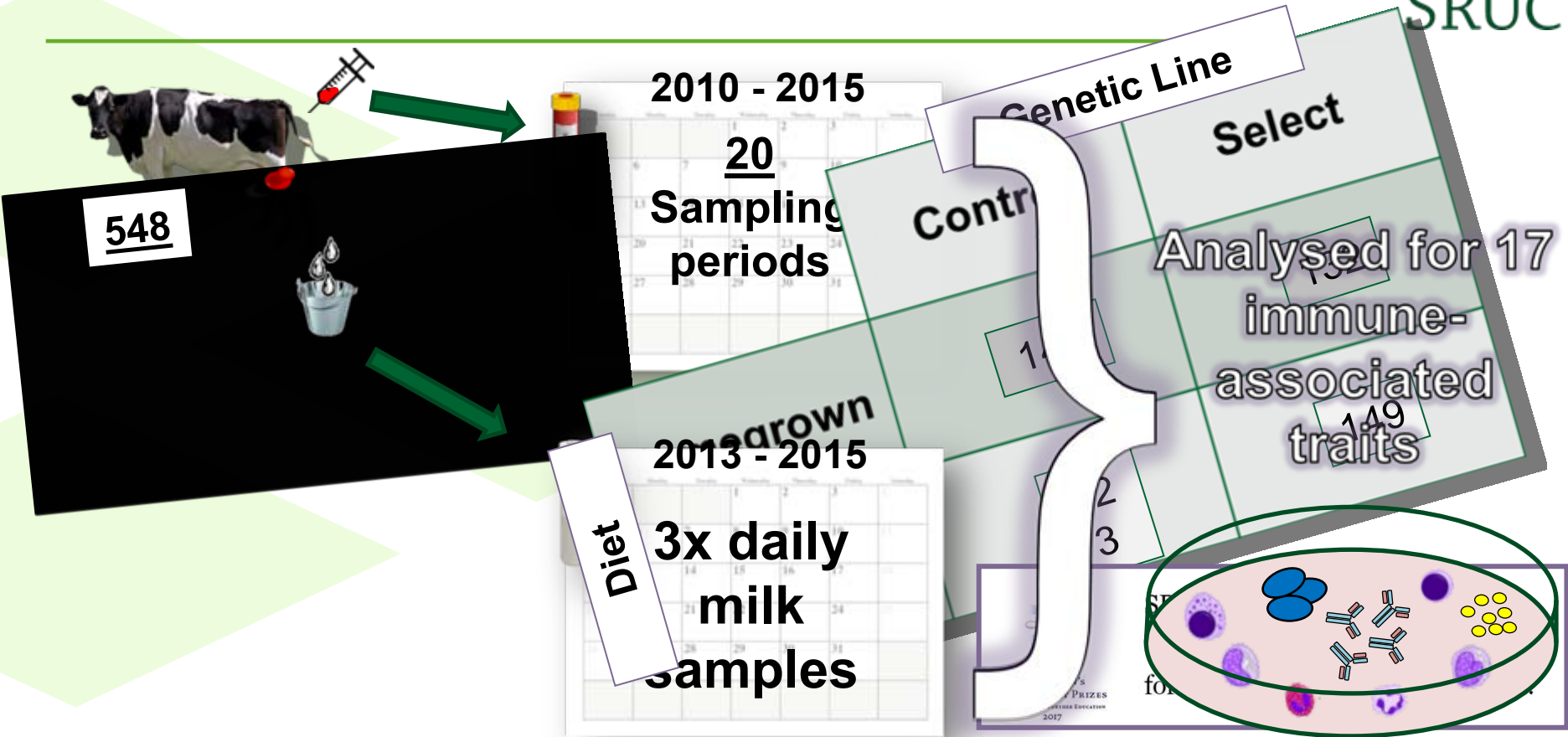PBMC   Eosinophils   Lymphocytes   Monocytes   Neutrophils   CD4+   CD8+   CD4:CD8 ratio   NKp46+

Objective

Can we determine genomic regions significantly associated with immune-associated traits?

Methods - Data collection

548

2010 - 2015

20 Sampling periods

2013 - 2015

3x daily milk samples

Diet

Homegrown

Genetic Line

Control

Select

Analysed for 17 immune-associated traits

Methods - Data collection

Trait	No. Records	Mean	Std. Dev
% PBMC	2,266	58.39	10.24
% Eosinophils	2,266	3.61	3.43
% Lymphocytes	2,265	44.25	12.35
% Monocytes	2,265	13.99	8.25
% Neutrophils	2,266	37.76	10.10
% CD4$^+$	2,232	25.52	6.28
% CD8$^+$	2,260	11.29	3.42
CD4$^+$:CD8$^+$ ratio	2,232	2.38	0.73
% NKp46$^+$	2,262	2.32	1.58

Trait	No. Records	Mean	Std. Dev
Hp (milk)	3,561	83.87	369.79
NAb$_{KLH}$ (blood)	2,687	0.94	0.30
NAb$_{LPS}$ (blood)	3,570	1.15	0.52
TNF-α (blood)	3,568	1,841.74	6,435.26
Hp (milk)	2,667	0.97	6.39
NAb$_{KLH}$ (milk)	2,667	0.81	0.35
NAb$_{LPS}$ (milk)	2,667	0.34	0.24
TNF-α (milk)	2,667	103.29	375.23

Methods - Genotyping
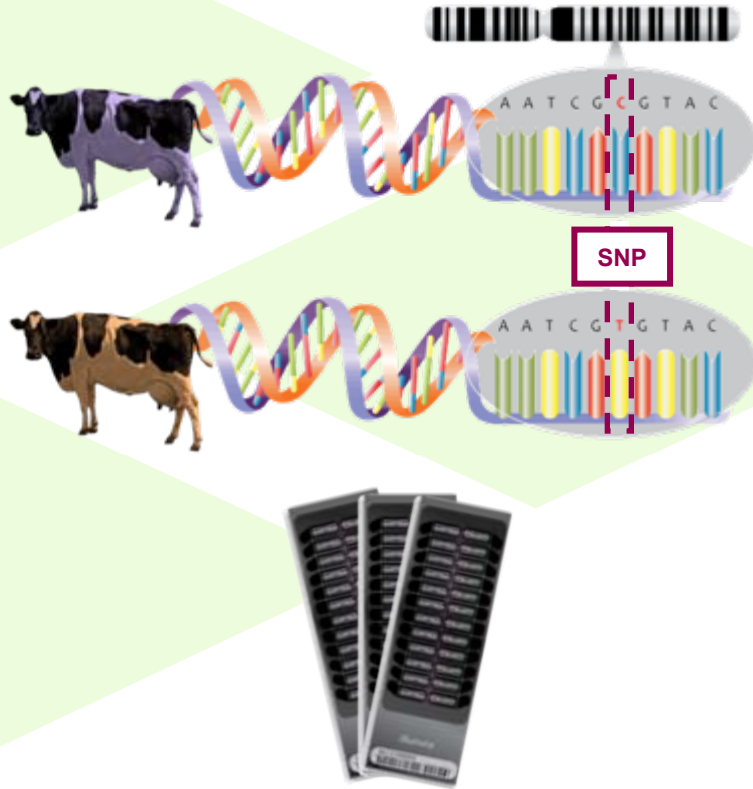
- **80% of cows** genotyped
  - Illumina **BovineSNP50** BeadChip

- **Remaining cows** genotyped
  - GeneSeek **GGP Bovine 150k** BeadChip

- 34,143 **common SNPs**

Methods – Quality control

- **SNP** QC applied
  - minor allele frequency (**MAF**) < 0.01
  - call rate < 95%

- **Sample** QC applied
  - call rate < 85%

Post QC:

- **1,637** SNPs removed
- **535** samples × **32,506** SNPs

- **13** samples removed

Methods - GWAS

- **EBV**s calculated via:

$$y = Xa + Z_1b + Z_2c + e$$

- De-regressed following **Garrick et al. (2009)**

- **dEBV**s used in single marker regression via:

$$y = \mu + Xg + e$$

- Fixed effects included:
  - diet group
  - genetic group
  - lactation week
  - assay technique
  - year by month of calving interaction
  - lactation number by age at calving interaction
  - random **additive genetic**
  - random **residual**

- Cow fitted as random effect
  - permanent environmental effect of cow also fitted (repeated measures)

y : **trait** observations

$$dEBV = \frac{EBV}{r^2}$$

a, b, c = **fixed effects** of the model, random **permanent environmental**

$r^2 = reliability\ of\ EBV$

X, Z_1, Z_2 = **incidence matrices**

$$weights = \left(\frac{1 - h^2}{c + \frac{1 - r^2}{r^2}} \right)_i$$

$c > 0$ is the fraction of genetic variance not explained by markers

Methods - GWAS

- **EBV**s calculated via:

$$y = Xa + Z_1b + Z_2c + e$$

- De-regressed following **Garrick et al. (2009)**

- **dEBV**s used in single marker regression via:

$$y = \mu + Xg + e$$

- y : vector of dEBV

- μ, g, e : overall mean, effect of SNP (coded 0, 1, 2) and residual error, respectively

- X : design matrix allocating records to SNP effects

Bonferroni correction
= *0.05 / number of SNPs*

False Discovery Rate (FDR)
= number of tests ✕ P-value / number significant SNPs
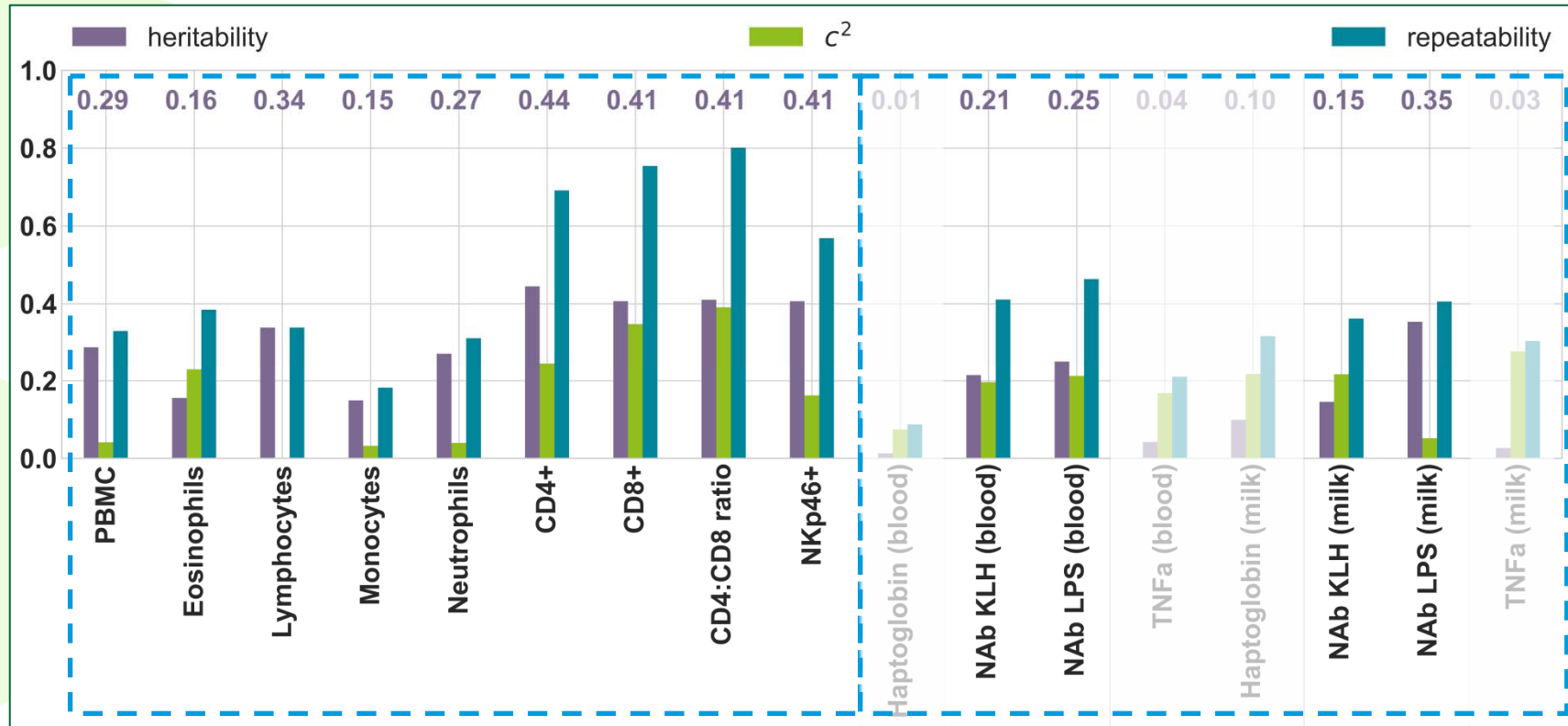
Methods – Functional analysis

- **Ensembl**[1] *Bos taurus* UMD3.1 assembly

- Genes within ±500kbp of SNP significantly associated with immune-associated traits

- **D**atabase for **A**nnotation, **V**isualization and **I**ntegrated **D**iscovery (**DAVID**[2]) v6.8

[1] https://www.ensembl.org, Yates et al. (2016)
[2] https://david.ncifcrf.gov, Huang et al. (2009)
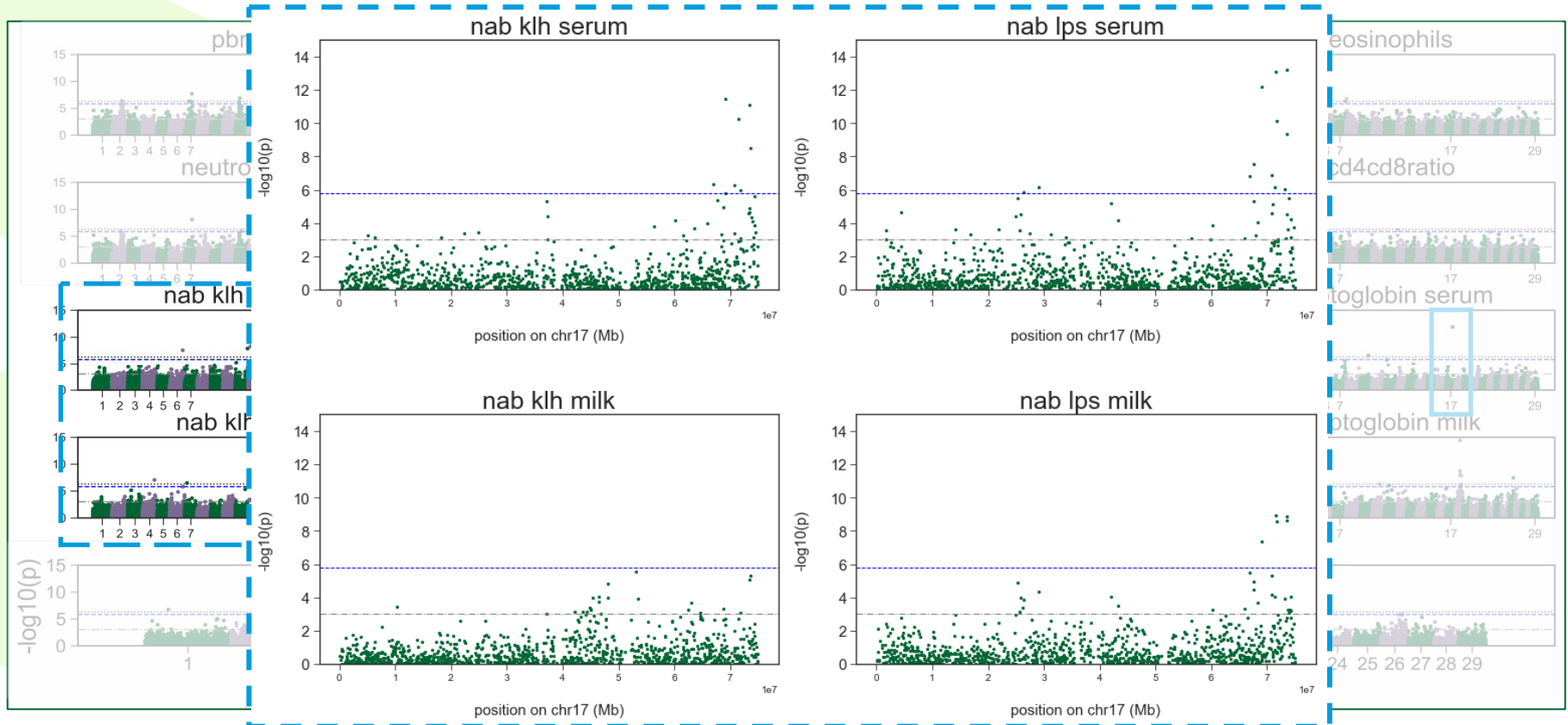
Results – Genetic analysis

Results – GWAS

Results – Functional analysis

- 9 clusters containing 122 genes were observed

- Significant associations with biological pathways also observed such as systemic lupus erythematosus
  - fat digestion and absorption
  - pancreatic secretion
  - tuberculosis

Cluster	Number of genes	Enrichment Score‡	Cluster names
1	10	3.6	phospholipases
2	6	3.1	Interleukins
3	9	2.4	Histone cluster proteins
4	54	1.1	olfactory receptor
5	6	1.0	homeobox
6	20	0.4	zinc finger protein
7	6	0.3	myelin associated glycoprotein
8	6	0.3	transmembrane proteins
9	5	0.3	transmembrane proteins

Conclusions

- Interesting and potentially novel genomic regions observed

- Highlighted several SNP significantly associated with various immune-associated traits
  – notably SNP associated with natural antibodies on chr17

- Identified potentially useful SNPs for enriching genotyping

Acknowledgements

Thanks for listening!

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