

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

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# Introduction



## • Low-cost genotyping technology

Animal (2012), 6:8, pp 1206–1215 © The Animal Consortium 2012  
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**Genome-wide associations for fertility traits in Holstein–Friesian dairy cows using data from experimental research herds in four European countries**

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Genetic parameters for predicted methane production and methane production from detector measurements<sup>1</sup>

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Open Access

Thompson-Crispi et al. BMC Genomics 2014, 15:559  
http://www.biomedcentral.com/1471-2164/15/559

RESEARCH ARTICLE

**A genome-wide association study of immune response traits in Canadian Holstein cattle**

Kathleen A Thompson-Crispi<sup>1,2\*</sup>, Mehdi Sargolzaei<sup>2,3</sup>, Ricardo Ventura<sup>2,4</sup>, Mohammed Abo-Ismael<sup>2,5</sup>, Filippo Miglior<sup>2,6</sup>, Flavio Schenkel<sup>2</sup> and Bonnie A Mallard<sup>1,2</sup>

OPEN ACCESS Freely available online

**A Genome Wide Association Study of Bovine Susceptibility in Holstein-Friesian Dairy Cattle**

Emma K. Finlay<sup>1</sup>, Donagh P. Berry<sup>2</sup>, Brian Wickham<sup>3</sup>, Eamonn P. Gormley<sup>4</sup>, Daniel G. Bradley<sup>1\*</sup>

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2010)

**Genetic cell score in first-lactation Holstein cows**

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# Introduction



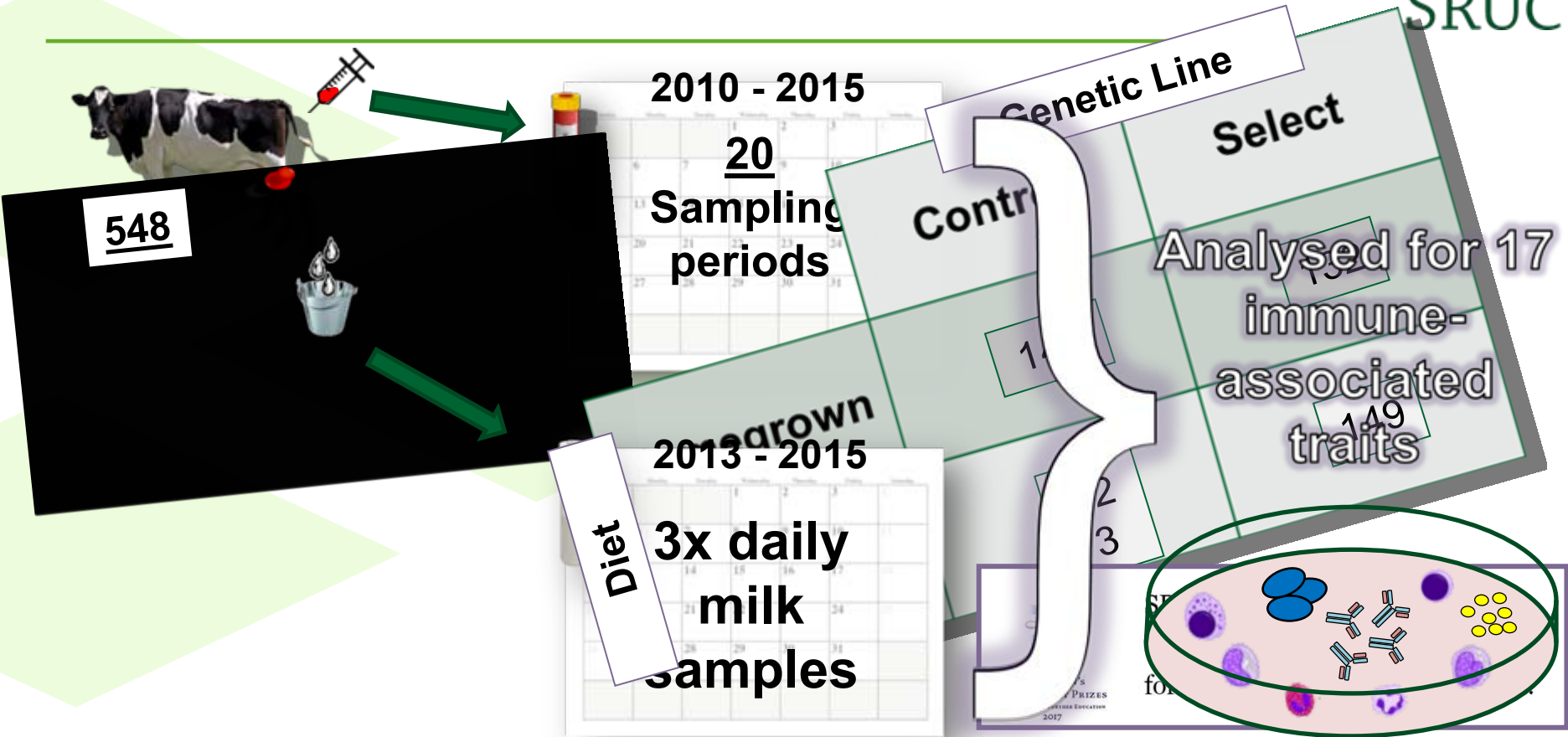
# Objective

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

# Methods - Data collection

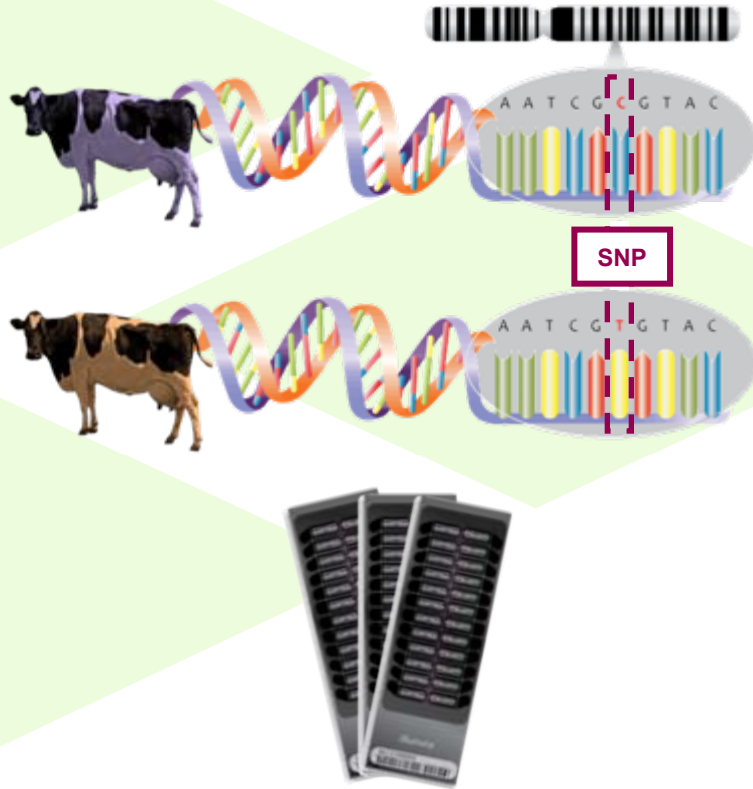


# Methods - Data collection

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 <sup>+</sup>	2,232	25.52	6.28
% CD8 <sup>+</sup>	2,260	11.29	3.42
CD4 <sup>+</sup> :CD8 <sup>+</sup> ratio	2,232	2.38	0.73
% NKp46 <sup>+</sup>	2,262	2.32	1.58

Trait	No. Records	Mean	Std. Dev
Hp (milk)	3,561	83.87	369.79
NAb <sub>KLH</sub> (blood)	2,687	0.94	0.30
NAb <sub>LPS</sub> (blood)	3,570	1.15	0.52
TNF- $\alpha$ (blood)	3,568	1,841.74	6,435.26
Hp (milk)	2,667	0.97	6.39
NAb <sub>KLH</sub> (milk)	2,667	0.81	0.35
NAb <sub>LPS</sub> (milk)	2,667	0.34	0.24
TNF- $\alpha$ (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

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- **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  $\times$  **32,506** SNPs
- **13** samples removed



# Methods - GWAS

- EBVs calculated via:

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

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

- dEBVs** used in single marker regression via:

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

- Fixed effects included:

- diet group
- trait observations  $\frac{EBV}{r^2}$
- genetic group
- lactation week

- $a, b, c, e$ 
  - assay technique
  - EBV hypothesis of calving interval
  - fixed effects of lactation week
  - lactation number by age at calving
  - random permanent environmental interaction
  - random additive genetic
  - random residual  $r^2 = \text{reliability of EBV}$

- Cow fitted as random effect

- permanent environmental effect of cow
- incidence matrices  $\left( \frac{1-h^2}{c+r^2} \right)_n$

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

# Methods - GWAS

- EBVs calculated via:

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

- **dEBVs** used in single marker regression via:

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

- $y$  : vector of dEBV
- $\mu, g, e$  : overall mean, effect of SNP (coded 0, 1, 2) and residual error, respectively
- $X$  : design matrix allocating records to SNP effects

Bonferroni correction

$$= 0.05 / \text{number of SNPs}$$

False Discovery Rate (FDR)

$$= \text{number of tests} \times \text{P-value} / \text{number significant SNPs}$$

# Methods – Functional analysis

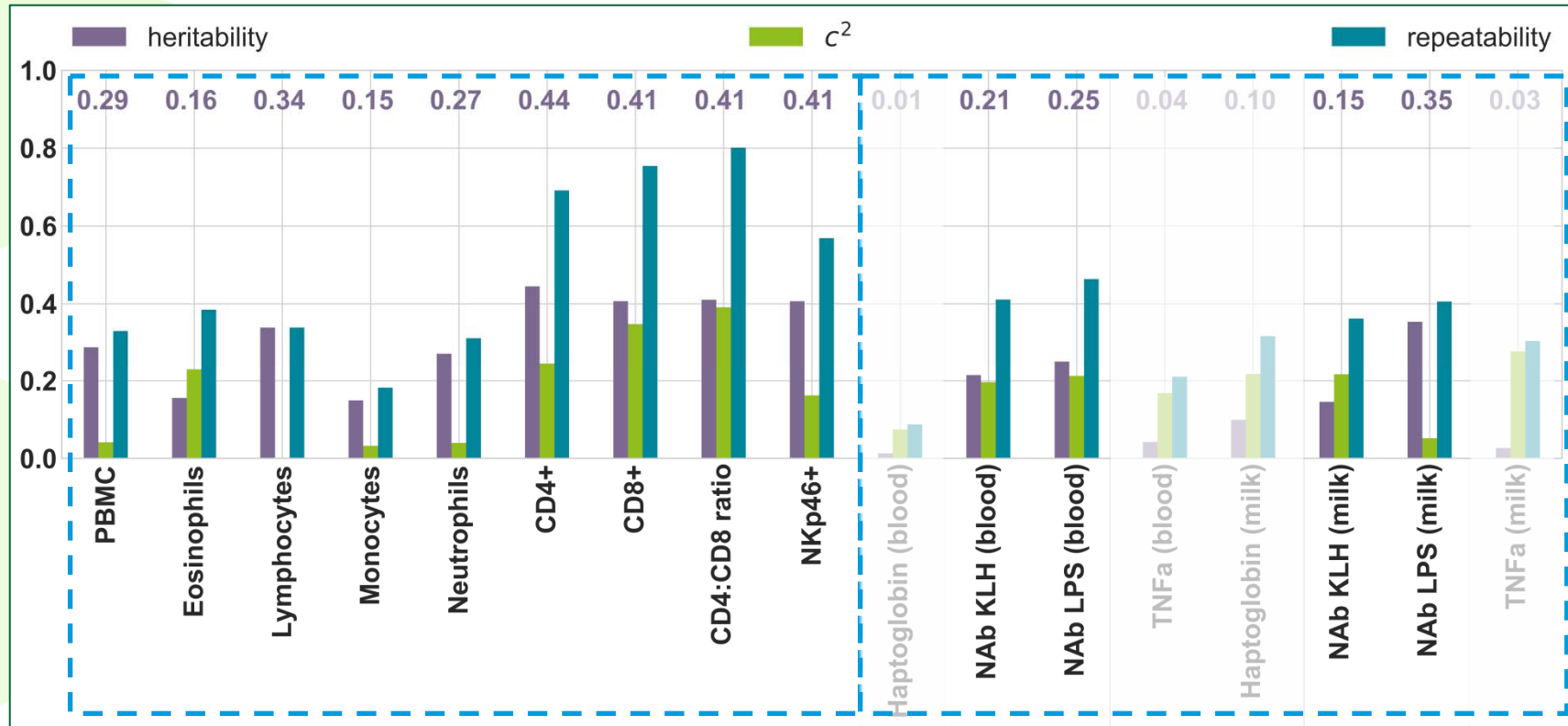
- **Ensembl**<sup>1</sup> *Bos taurus* UMD3.1 assembly
- Genes within  $\pm 500$  kbp of SNP significantly associated with immune-associated traits
- Database for **Annotation, Visualization and Integrated Discovery (DAVID)**<sup>2</sup> v6.8



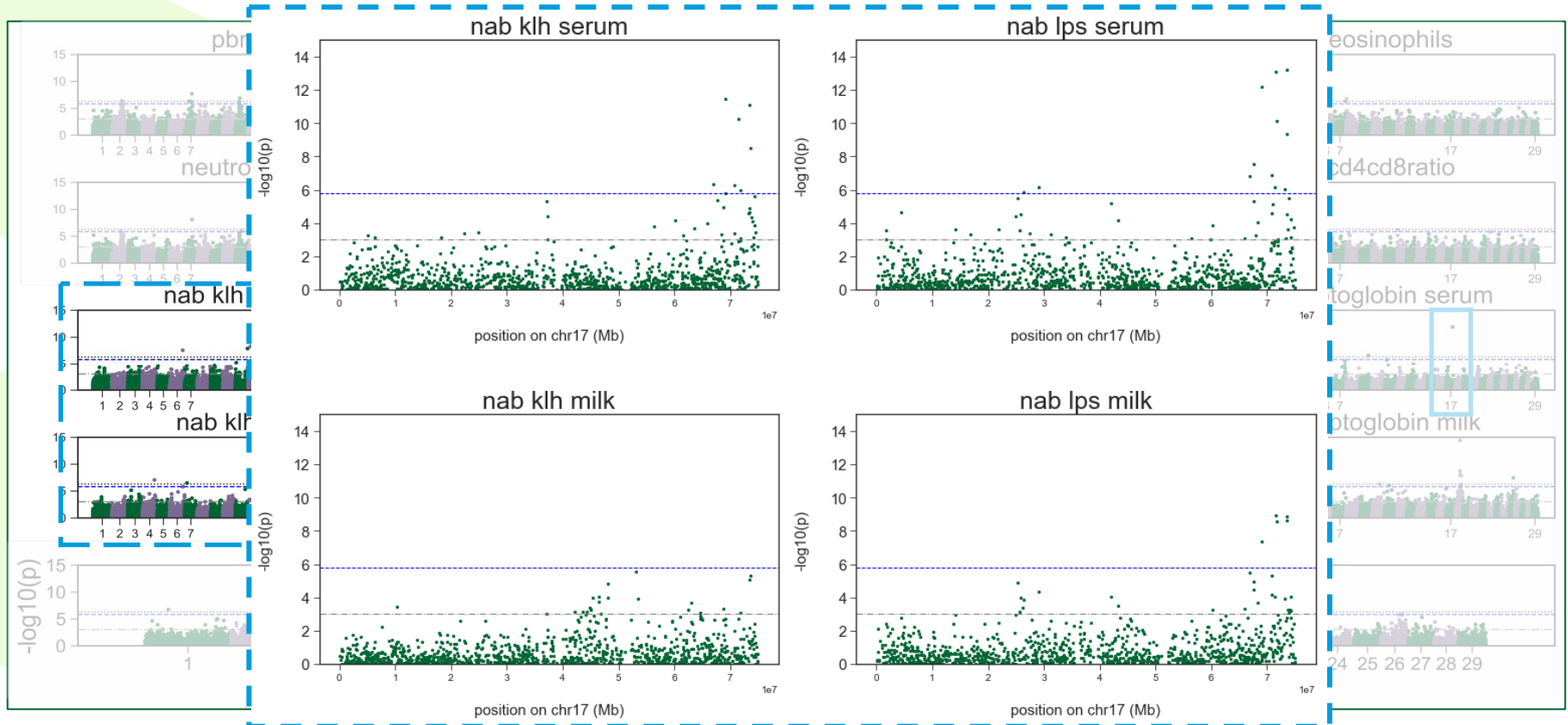
<sup>1</sup> <https://www.ensembl.org>, Yates et al. (2016)

<sup>2</sup> <https://david.ncifcrf.gov>, Huang et al. (2009)

# Results – Genetic analysis



# Results – GWAS



# Results – Functional analysis

- 9 clusters containing 122 genes were observed

‡ geometric mean (-log scale) of member's p-values in corresponding annotation cluster, used to rank biological significance. The top ranked annotation groups most likely have consistent lower p-values for their annotation members (Huang et al., 2009)

Cluster	Number of genes	Enrichment Score†	Cluster names
1	10	3.0	fat digestion and absorption
2	6	3.1	phospholipases
3	9	2.4	Interleukins
4	54	2.4	pancreatic secretion
5	6	1.0	Histone cluster proteins
6	20	0.4	olfactory receptor
7	6	0.3	tuberculosis
8	6	0.3	homeobox
9	5	0.3	zinc finger protein
			myelin associated glycoprotein
			transmembrane proteins
			transmembrane proteins

- Significant associations with biological pathways also observed such as systemic lupus erythematosus

# Conclusions

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- 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

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# Thanks for listening!

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