Genome-wide association study in colostrum reveals QTL for natural antibodies in Swedish dairy cattle

J. Cordero, J.J. Wensman, M. Tråvén, J.A.J. Arts, H.K. Parmentier, H. Bovenhuis & D.J. de Koning

Problem

Failure of passive transfer – FPT (Bielmann et al., 2010, Tyler et al., 1996)

- Low IgG content in serum at age 24-48 h. Cutoff IgG 10 g/L or STP 52-55 g/L
- Increased risk of mortality, ↓ health
- Delayed time to first calving, ↓ milk and fat production at first lactation
- €60 (10-109) per calf (Raboisson et al., 2016)

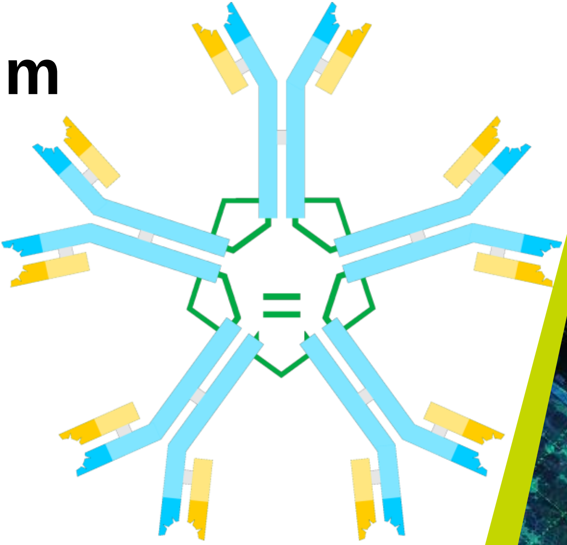
Sweden, calf mortality 5.6%

- Before weaning
- High proportion of FPT in Swedish herds (30-50%) (Hertel 2012; Silverlås et al., 2010; Torsein et al., 2011)

Target of this study

Natural Antibodies (NAbs) in Colostrum

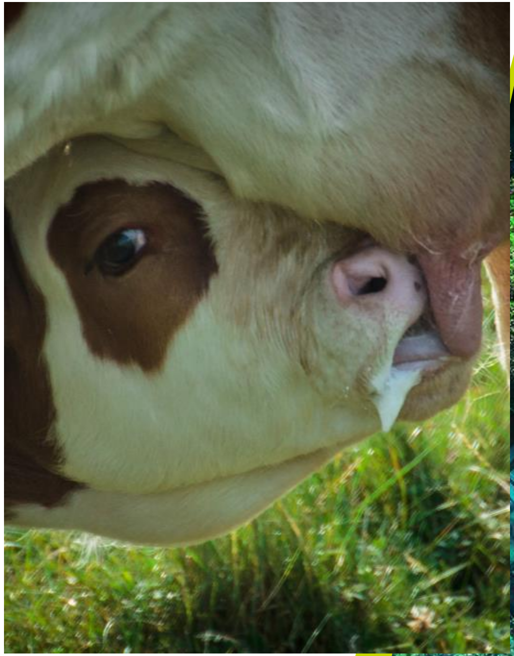
- *Innate immunity*
  - No previous exposure
  - Polyreactive, low binding affinity
    - PAMPs
    - Autoantigens



Background

Natural Antibodies (NAbs)

- Heritabilities (Ploegaert *et al*. 2010, Wijga *et al.* 2013, De Klerk *et al*. 2018, Denholm *et al.* 2018)
  - IgG → 0.08 – 0.40
  - IgM → 0.18 – 0.45
  - IgA → 0.30 – 0.55



Methodology

- Sampling, Jan 2015 to Apr 2017
- 3 farms (Lövsta, Röbäcksdalen, Viken)
- Swedish Red (70%)
- Holstein (30%)

Methodology

1313 Cows, 1 to 7 parities

- Colostrum (1719 samples)
  - IgG estimate (% Brix Refractometer)
  - IgG g/L measurement (ELISA)
  - NAbs, KLH and MDP (IgM, IgG, IgA) – ELISA

- Information
  - Calving to colostrum sampling (min)

Methodology

- Linear mixed model
  - ASReml 4.1
- Pedigree
  - Växa Sweden
  - 20 generations
- Genotypes
  - LD 7K imputed to 50K (NAV)
- Variance proportions, genetic correlations and GWAS

Methodology

Colostrum model

$$y_{ijkl} = \mu + \beta_1 Tim_{ijklm} + Par_i + Brd_j + HYSP_k + a_l + pe_m + e_{ijklm}$$

Fixed

- $\beta_1 Tim_{ijklm}$: Calving to colostrum sampling time
- Par_i: Parity
- Brd_j: Breed

Random

- $HYSP_k$: **H**erd-**Y**ear-**S**eason of calving and sample storage **P**late
- a_l: Additive genetic effect
- pe_m: Permanent environment effect

Methodology

GWAS model

$$y_{ijkl} = \mu + SNP_i + \beta_1 Tim_{ijklm} + Par_i + Brd_j + HYSP_k + a_l + pe_m + e_{ijklm}$$

Fixed

SNP_i: Genotype
$\beta_1 Tim_{ijklm}$: Calving to colostrum sampling time
Par_i: Parity
Brd_j: Breed

Random

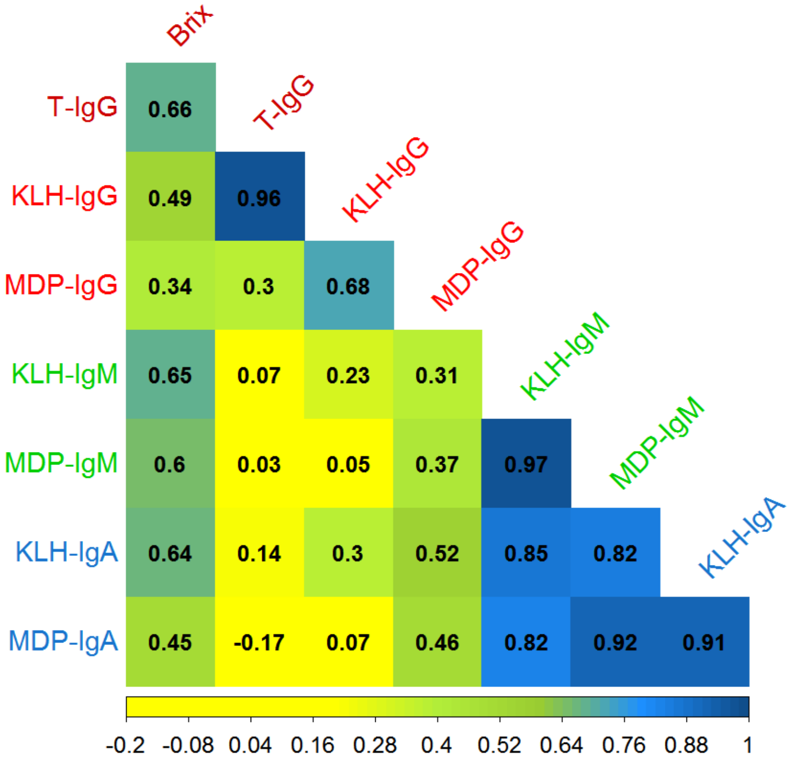
$HYSP_k$: **H**erd-**Y**ear-**S**eason of calving and sample storage **P**late
a_l: Additive genetic effect
pe_m: Permanent environment effect

Heritabilities

Trait	h^2	rep
Brix (%)	**0.28** (0.07)	0.40 (0.04)
Total-IgG (g/L)	**0.20** (0.09)	0.26 (0.07)
KLH-IgG	**0.13** (0.06)	0.47 (0.04)
MDP-IgG	**0.22** (0.06)	0.55 (0.03)
KLH-IgM	**0.25** (0.07)	0.44 (0.04)
MDP-IgM	**0.22** (0.06)	0.40 (0.04)
KLH-IgA	**0.24** (0.06)	0.46 (0.04)
MDP-IgA	**0.25** (0.06)	0.38 (0.04)

Results

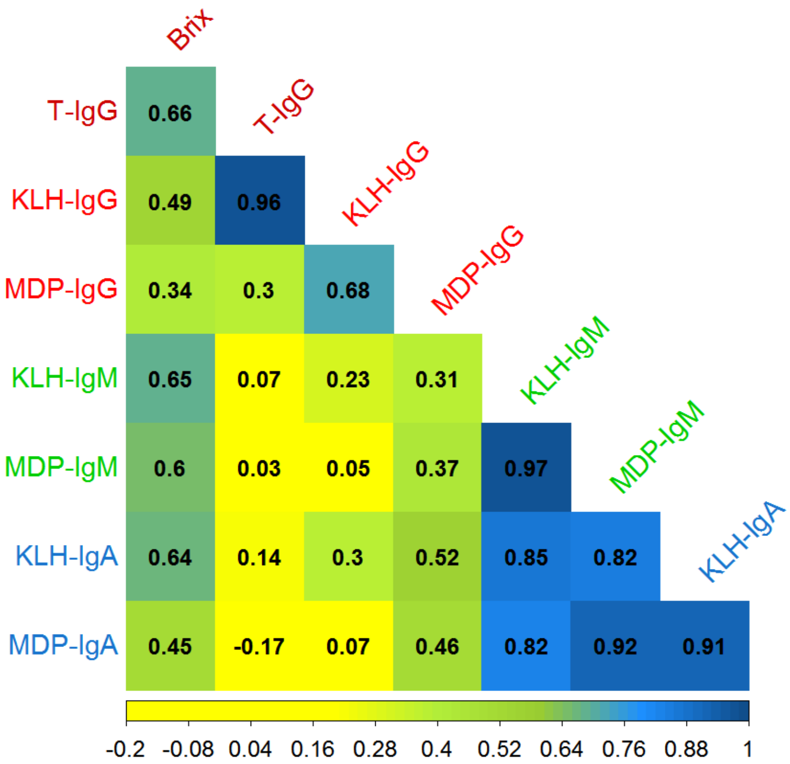
Genetic correlations of colostrum Brix and NAb titers



	Brix	T-IgG	KLH-IgG	MDP-IgG	KLH-IgM	MDP-IgM	KLH-IgA
T-IgG	0.66						
KLH-IgG	0.49	0.96					
MDP-IgG	0.34	0.3	0.68				
KLH-IgM	0.65	0.07	0.23	0.31			
MDP-IgM	0.6	0.03	0.05	0.37	0.97		
KLH-IgA	0.64	0.14	0.3	0.52	0.85	0.82	
MDP-IgA	0.45	-0.17	0.07	0.46	0.82	0.92	0.91

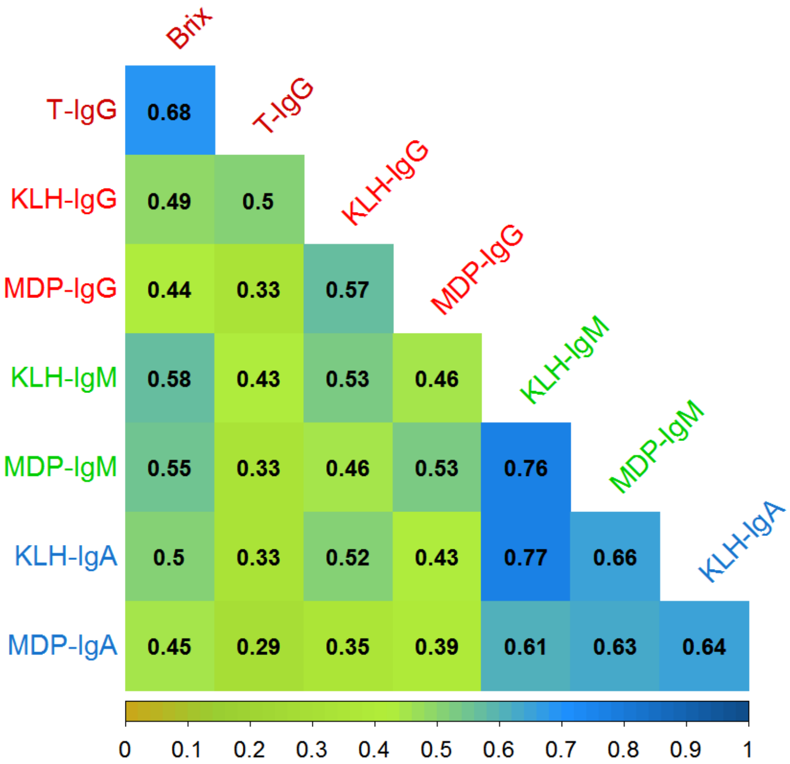
Correlations

Genetic correlations of colostrum Brix and NAb titers



	Brix	T-IgG	KLH-IgG	MDP-IgG	KLH-IgM	MDP-IgM	KLH-IgA
T-IgG	0.66						
KLH-IgG	0.49	0.96					
MDP-IgG	0.34	0.3	0.68				
KLH-IgM	0.65	0.07	0.23	0.31			
MDP-IgM	0.6	0.03	0.05	0.37	0.97		
KLH-IgA	0.64	0.14	0.3	0.52	0.85	0.82	
MDP-IgA	0.45	-0.17	0.07	0.46	0.82	0.92	0.91

Phenotypic correlations of colostrum Brix and NAb titers



	Brix	T-IgG	KLH-IgG	MDP-IgG	KLH-IgM	MDP-IgM	KLH-IgA
T-IgG	0.68						
KLH-IgG	0.49	0.5					
MDP-IgG	0.44	0.33	0.57				
KLH-IgM	0.58	0.43	0.53	0.46			
MDP-IgM	0.55	0.33	0.46	0.53	0.76		
KLH-IgA	0.5	0.33	0.52	0.43	0.77	0.66	
MDP-IgA	0.45	0.29	0.35	0.39	0.61	0.63	0.64

Correlations with production traits

Trait	Brix	T-IgG	IgG-KLH	IgG-MDP	IgM-KLH	IgM-MDP	IgA-KLH	IgA-MDP
Milk yield	**0.18 (0.16)**	**0.54 (0.29)**	0.2 (0.23)	0.13 (0.18)	-0.07 (0.18)	-0.16 (0.18)	-0.03 (0.17)	0.05 (0.17)

Correlations with production traits

Trait	Brix	T-IgG	IgG-KLH	IgG-MDP	IgM-KLH	IgM-MDP	IgA-KLH	IgA-MDP
Milk yield	**0.18 (0.16)**	**0.54 (0.29)**	0.2 (0.23)	0.13 (0.18)	-0.07 (0.18)	-0.16 (0.18)	-0.03 (0.17)	0.05 (0.17)
Protein	0.04 (0.15)	0.16 (0.24)	0.03 (0.21)	0.16 (0.17)	**0.34 (0.17)**	**0.36 (0.16)**	**0.25 (0.16)**	**0.38 (0.15)**

Correlations with production traits

Trait	Brix	T-IgG	IgG-KLH	IgG-MDP	IgM-KLH	IgM-MDP	IgA-KLH	IgA-MDP
Milk yield	**0.18 (0.16)**	**0.54 (0.29)**	0.2 (0.23)	0.13 (0.18)	-0.07 (0.18)	-0.16 (0.18)	-0.03 (0.17)	0.05 (0.17)
Protein	0.04 (0.15)	0.16 (0.24)	0.03 (0.21)	0.16 (0.17)	**0.34 (0.17)**	**0.36 (0.16)**	**0.25 (0.16)**	**0.38 (0.15)**
Fat	-0.09 (0.18)	0.03 (0.28)	**-0.36 (0.23)**	-0.01 (0.19)	0.13 (0.19)	0.17 (0.19)	0.08 (0.19)	0.14 (0.19)

Correlations with production traits

Trait	Brix	T-IgG	IgG-KLH	IgG-MDP	IgM-KLH	IgM-MDP	IgA-KLH	IgA-MDP
Milk yield	**0.18 (0.16)**	**0.54 (0.29)**	0.2 (0.23)	0.13 (0.18)	-0.07 (0.18)	-0.16 (0.18)	-0.03 (0.17)	0.05 (0.17)
Protein	0.04 (0.15)	0.16 (0.24)	0.03 (0.21)	0.16 (0.17)	**0.34 (0.17)**	**0.36 (0.16)**	**0.25 (0.16)**	**0.38 (0.15)**
Fat	-0.09 (0.18)	0.03 (0.28)	**-0.36 (0.23)**	-0.01 (0.19)	0.13 (0.19)	0.17 (0.19)	0.08 (0.19)	0.14 (0.19)
SCC	**-0.5 (0.41)**	**-0.6 (0.58)**	**-0.62 (0.47)**	0.31 (0.59)	**-0.55 (0.50)**	**-0.65 (0.49)**	-0.37 (0.45)	-0.18 (0.44)

Correlations with production traits

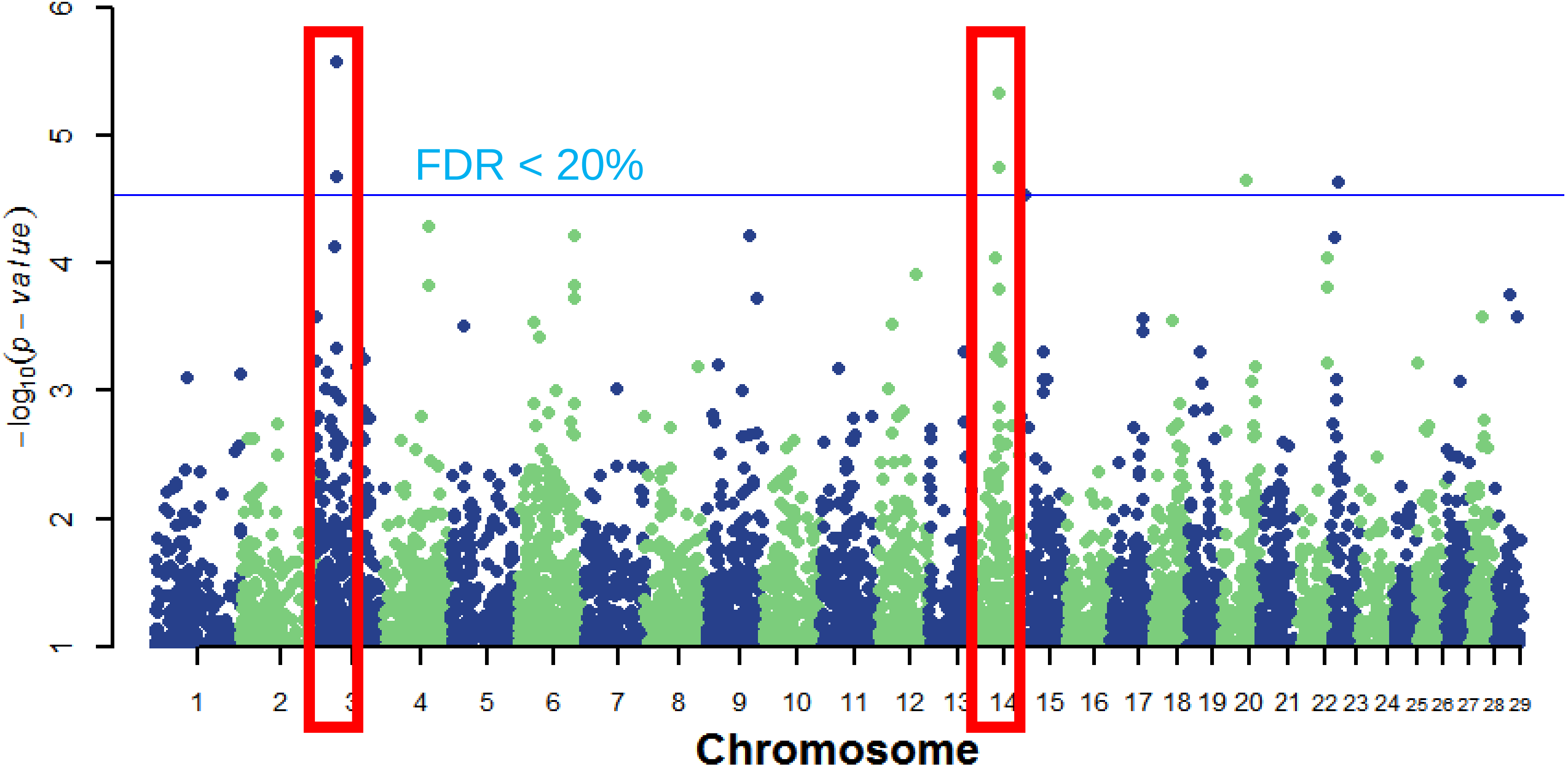
Trait	Brix	T-IgG	IgG-KLH	IgG-MDP	IgM-KLH	IgM-MDP	IgA-KLH	IgA-MDP
Milk yield	**0.18 (0.16)**	**0.54 (0.29)**	0.2 (0.23)	0.13 (0.18)	-0.07 (0.18)	-0.16 (0.18)	-0.03 (0.17)	0.05 (0.17)
Protein	0.04 (0.15)	0.16 (0.24)	0.03 (0.21)	0.16 (0.17)	**0.34 (0.17)**	**0.36 (0.16)**	**0.25 (0.16)**	**0.38 (0.15)**
Fat	-0.09 (0.18)	0.03 (0.28)	**-0.36 (0.23)**	-0.01 (0.19)	0.13 (0.19)	0.17 (0.19)	0.08 (0.19)	0.14 (0.19)
SCC	**-0.5 (0.41)**	**-0.6 (0.58)**	**-0.62 (0.47)**	0.31 (0.59)	**-0.55 (0.50)**	**-0.65 (0.49)**	-0.37 (0.45)	-0.18 (0.44)
Urea	-0.12 (0.23)	0.13 (0.35)	-0.12 (0.31)	**-0.57 (0.26)**	0.14 (0.26)	0.04 (0.25)	0.07 (0.24)	-0.02 (0.24)

GWAS

Genomic regions

- Brix
  - BTA3 (37-41 Mbp)
  - BTA14 (44-48 Mbp)
- MDP-IgG
  - BTA20 (53-59 Mbp)
- MDP-IgM
  - BTA3 (96-100 Mbp)
- MDP-IgA
  - BTA21 (42-46 Mbp)

Brix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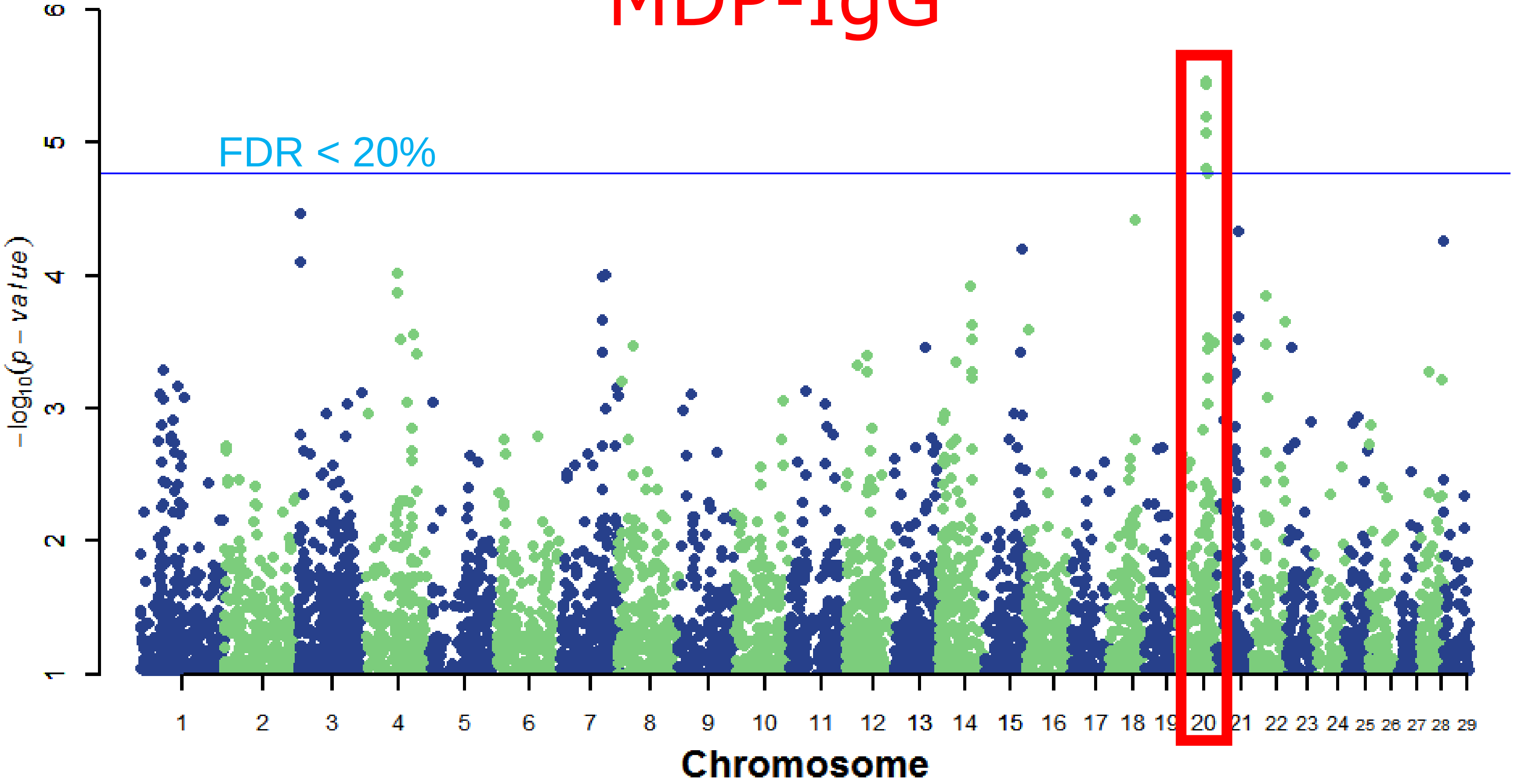
Chromosome

Chromosome 3 - Brix

- Lead SNP → BTB-01737920 (39,360,570 bp)
    - $-\log_{10}P = 5.6$
- Same region as Kiser *et al*. (2019) for colostrum Brix in Jersey and Leach *et al*. (2012) for serum IgG2 against Bovine Respiratory Syncytial Virus
- No clear candidate genes

MDP-IgG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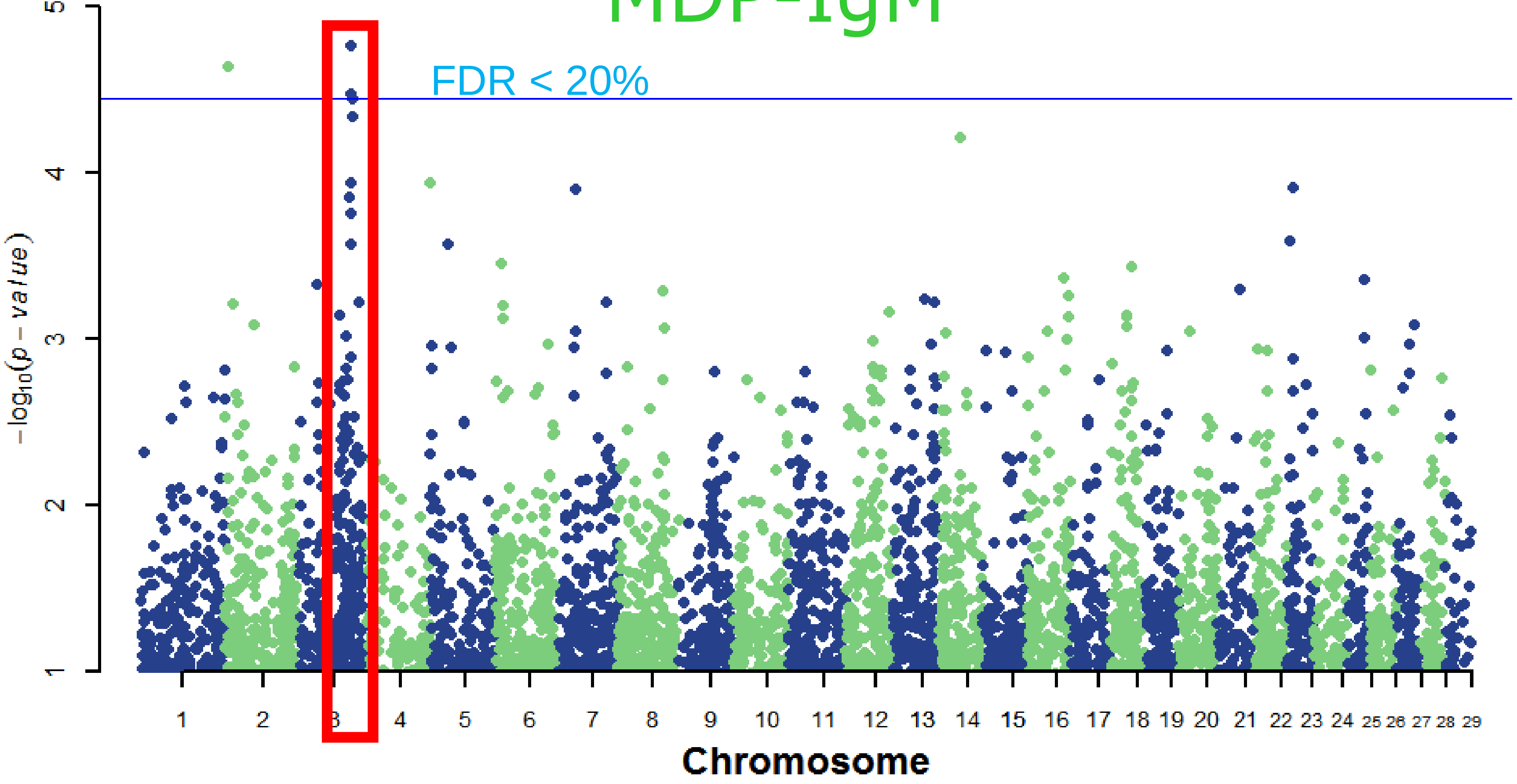
Chromosome 20 - MDP-IgG

- Lead SNP → BTB-00788621 (53,906,202 bp)
    - $-\log_{10}P = 5.5$
- Same region as de Klerk *et al*. (2018) for serum KLH-IgG
- Candidate genes
    - MYO10 – myosin X (Fc gamma R-mediated phagocytosis)
    - CDH18 – cadherin 18 (Cell-cell adhesion)

MDP-IgM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Chromosome

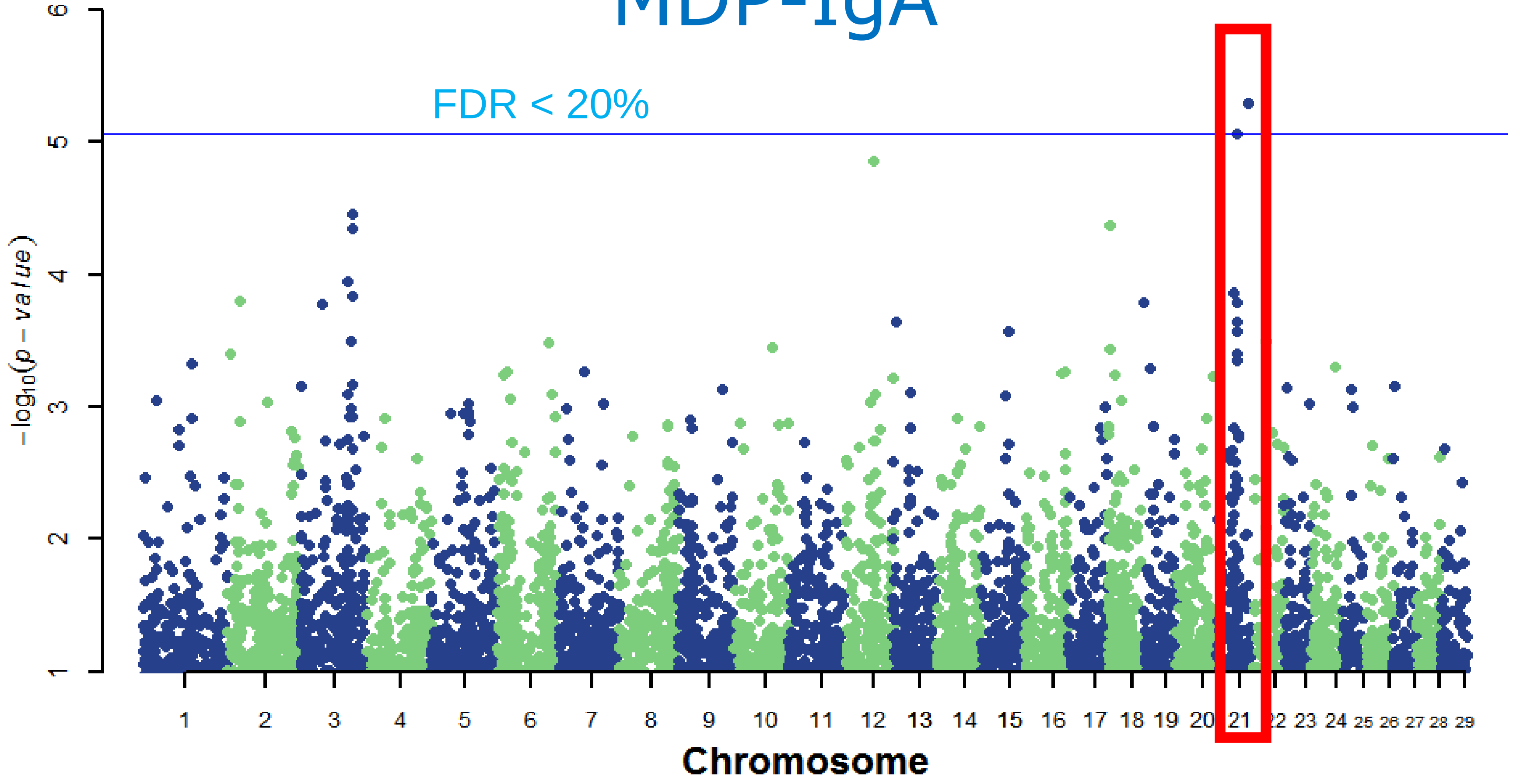
Chromosome 3 - MDP-IgM

- Lead SNP → BTB-00962714 (99,655,499 bp)
  - $-\log_{10}P = 4.8$

- Same region as de Neupane *et al*. (2018) for Bovine respiratory disease

- Candidate gene
  - MKNK1 - MAPK interacting serine/threonine kinase 1 (Interleukin signaling pathway)

MDP-IgA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Chromosome

Chromosome 21 - MDP-IgA

- Lead SNP → BTB-00820947 (44,634,072 bp)
    - $-\log_{10}P = 5.1$

- Candidate gene
    - NFKBIA - NFKB inhibitor alpha (B cell activation and signalling pathway)

Conclusions

- Moderate heritabilities
- Brix, T-IgG and NAb content can be selected
- Favourable correlations with production traits
- Genomic regions related to immunity
- Reasonable results with imputed data. HD highly desired

SLU

WAGENINGEN UR
For quality of life

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