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Swedish University of Agricultural Sciences



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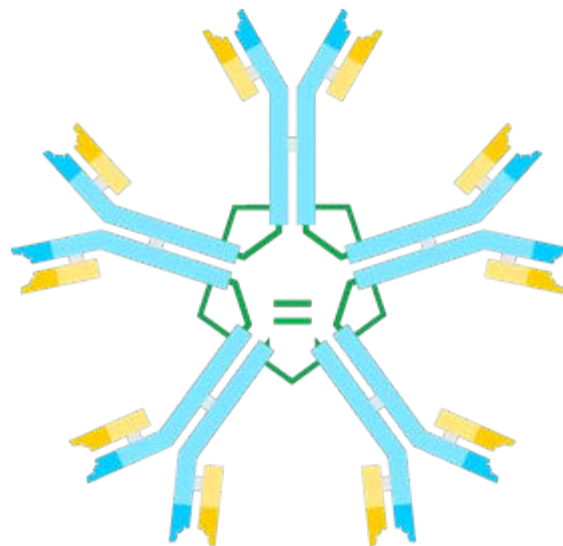
Stiftelsen  
Lantbruksforskning

# *Detection of candidate regions affecting bovine IgM natural antibodies in milk*

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WCGALP, February 12th 2018

# Background

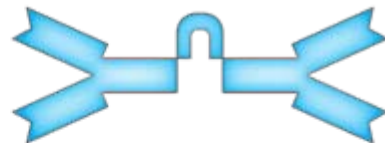
- **Specific Antibodies (SpAb)**
  - *Adaptive immunity*
    - Response to pathogen
    - Highly specific
  
- **Natural Antibodies (NAb)**
  - *Innate immunity*
    - No previous exposure
    - Polyreactive, low binding affinity
      - PAMPs
      - Autoantigens



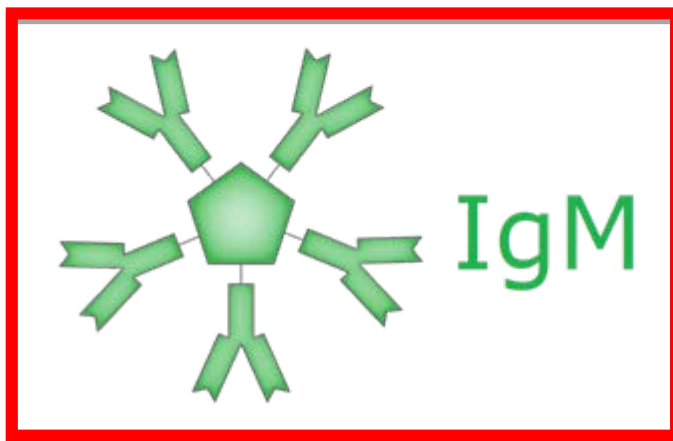
## Antibody isotypes



IgG



IgA



IgM

# Background

## Genetic parameters

- NAb (Ploegaert *et al.*, 2010, Wijga *et al.* 2013, De Klerk *et al.* TBS)

-  → 0.08 – 0.40

-  → 0.39 – 0.45

-  → 0.30 – 0.55

- IgA and IgM high genetic correlation



# *Background*

## **Humoral response (Antibodies)**

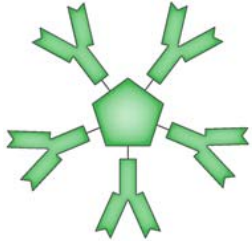
- SpAb
  - Mastitis (Rupp *et al.* 2007, Thompson-Crispi *et al.* 2012)
  - Paratuberculosis (Gonda *et al.* 2007, Minoza *et al.* 2010)
  - Nematodes (Morris *et al.* 2002, Hayhurst *et al.* 2010)
  
- NAb
  - Productive life (De Klerk *et al.* TBS)
  - Longer survival (Sun *et al.* 2011)
  - *E. coli* resistance (Berghof *et al.* TBS)

# *Background*

## Lipoteichoic acid (LTA)

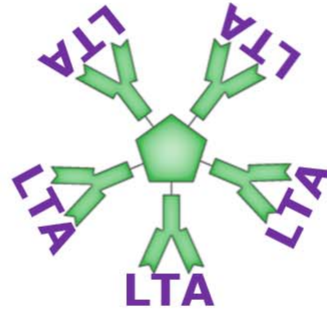
- Pathogen-associated molecular patterns (PAMPs)
- Cell wall of Gram+ bacteria
  - *Staphylococcus aureus*
- Immunostimulant

# IgM



LTA LTA LTA  
LTA LTA LTA

# LTA-Binding IgM





# *Materials and methods*

## **Animals and phenotypes**

- Dutch Milk Genomics Initiative (Stoop *et al.* 2008)

- 1630 Holstein-Friesian cows
- 379 herds
- 66 to 263 DIM (166 avg.)
- First calving

- NAb titers – Milk (Ploegaert *et al.* 2010)

- Indirect ELISA
- LTA-IgM

# *Materials and methods*

## **GWAS**

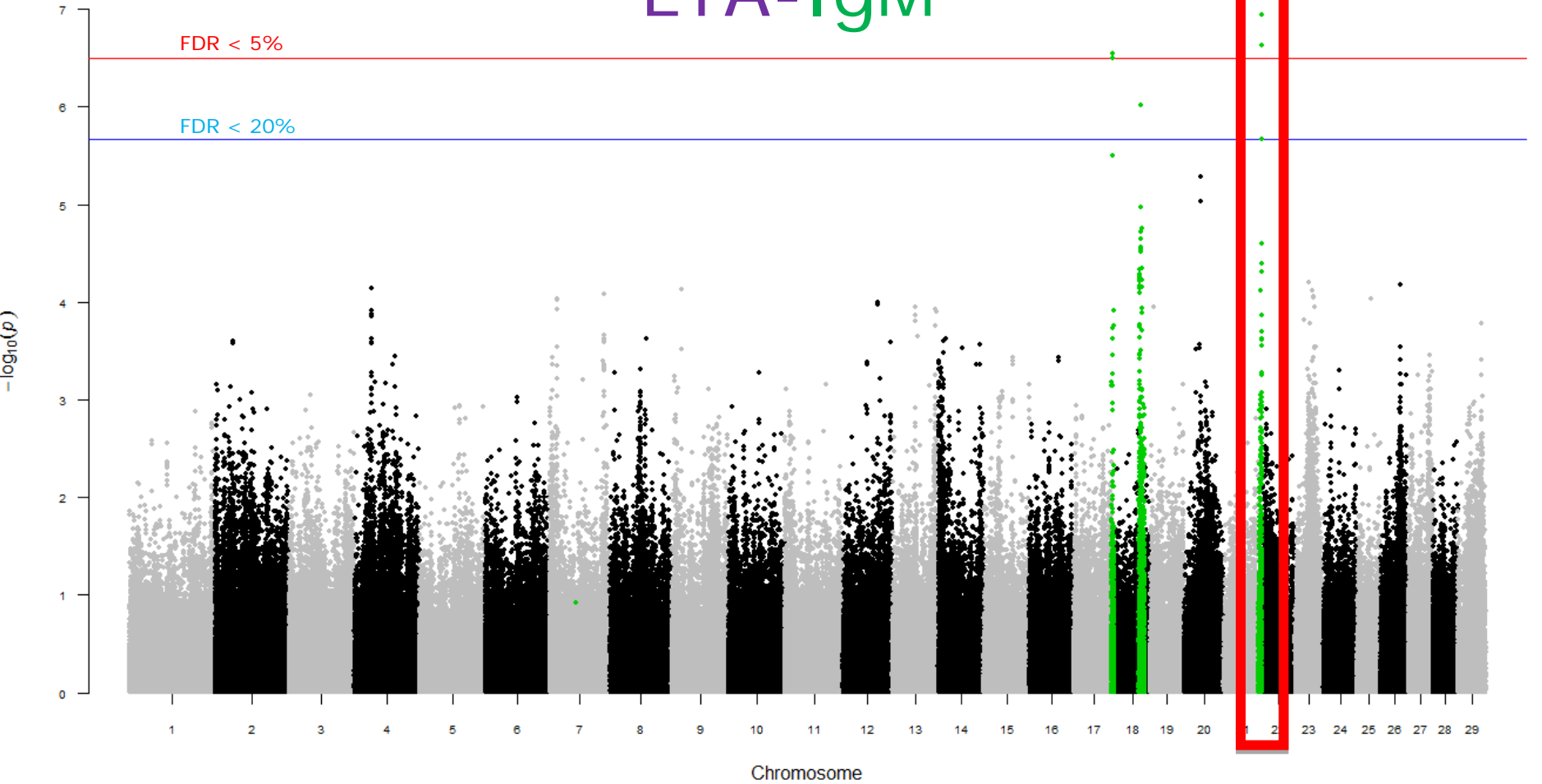
- Genotypes
  - Imputed 777K from 50K SNP chip
  - 576K
- Animal model (Schopen *et al.* 2011)
  - ASReml 4.1
  - Pedigree (4 generations)
  - Environmental effects
  - SNP as fixed effect

# *Results*

## **Genomic regions (200kb)**

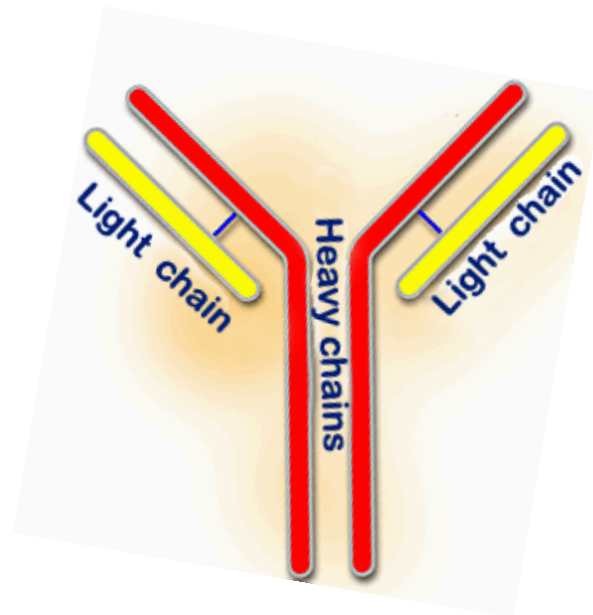
- Two significant
  - BTA21, 71.2 – 71.6 Mb (4 SNPs)
  - BTA17, 72.9 – 73.3 Mb (2 SNPs)
- One suggestive
  - BTA18, 49.6 – 50.0 Mb (1 SNP)

# LTA-IgM

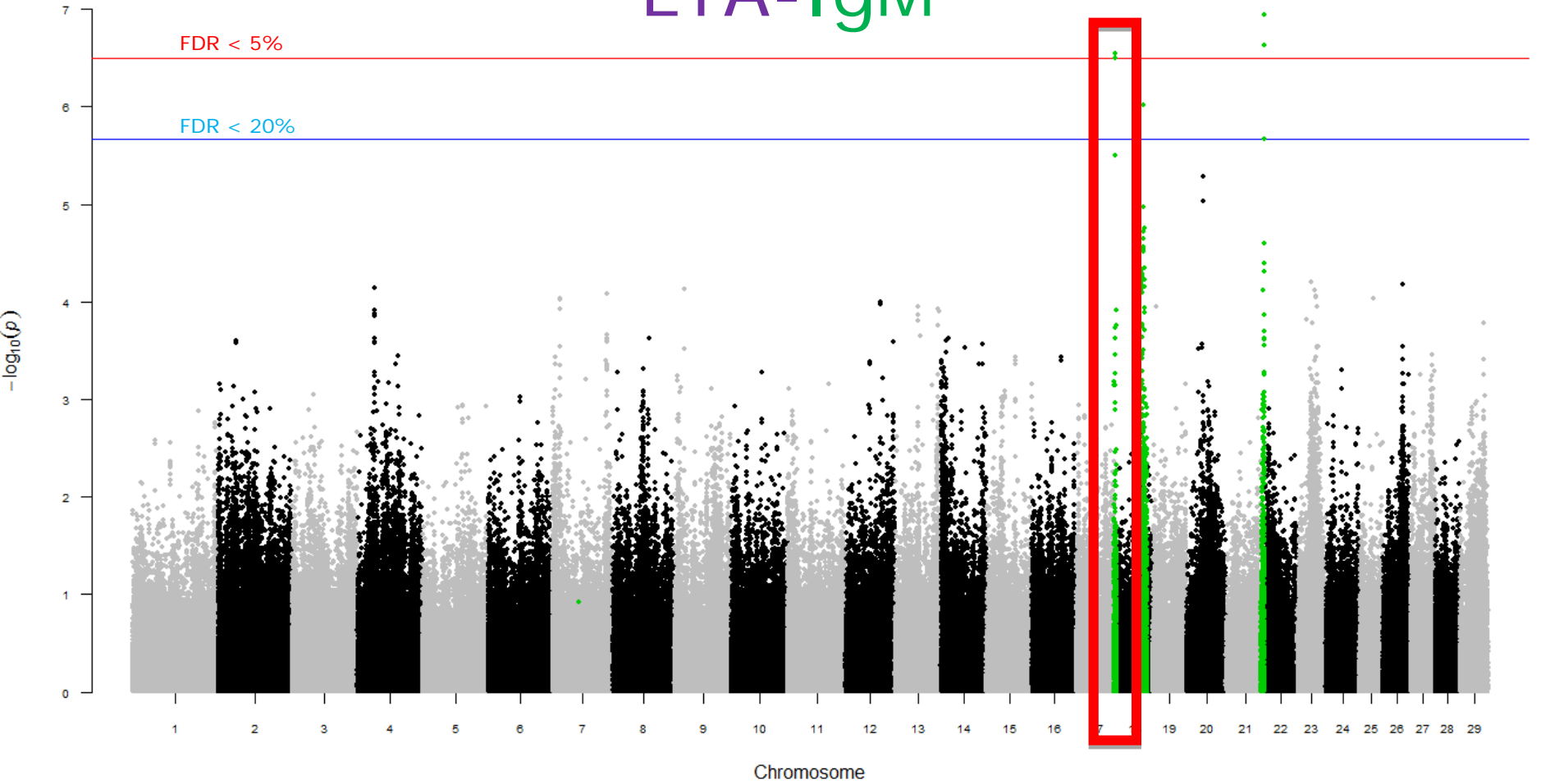


# Chromosome 21 - *IgM*

- Lead SNP → BovineHD2100020886 (71,482,201 bp)
  - $-\log_{10}P = 6.9$
  
- Candidate genes
  - IGHV - Immunoglobulin Heavy Locus
  - IGHV1S20 - Ig heavy chain V region PJ14
  - IGHV1S18 - Ig heavy chain Mem5-like

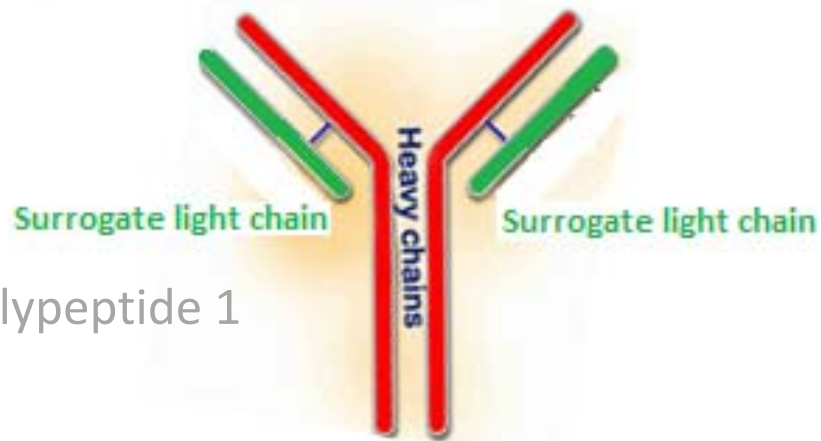


# LTA-IgM



# Chromosome 17 - *IgM*

- Lead SNP → BovineHD1700021382 (73,125,915 bp)
  - $-\log_{10}P = 6.5$
- Candidate genes
  - VPREB3 - pre-B lymphocyte 3
  - VPREB2 - pre-B lymphocyte 2
  - IGLL1 - Immunoglobulin lambda-like polypeptide 1



# *Conclusions*

- Genomic regions contain genes related to B cell development and immunoglobulins synthesis
- Analyse other antigens and isotypes
- Further studies should help understand the relationship between NAbs and health traits in dairy cows



*Thank you!*



Linear mixed model:

$$y_{ijklmno} = \mu + \beta_1 dim_{ijklmno} + \beta_2 e^{-0.05 * dim_{ijklmno}} + \beta_3 ca_{ijklmno} + \beta_4 ca_{ijklmno}^2 + season_k + scode_l + SNP_m + herd_n + animal_o + e_{ijklmno}$$

*Table 1. Lead SNP of each chromosome with suggestive or significant associations with LTA-IgM.*

SNP	rs ID	chr	Position	MAF <sup>1</sup>	Major/minor allele	Genotype effect (SE)	-log <sub>10</sub> P value
BovineHD2100020886	rs135338912	21	71482201	0.30	C/T	CC: -0.17 (0.05) TT: 0.34 (0.07)	6.9
BovineHD1700021382	rs133519711	17	73125915	0.10	A/G	AA: 0.35 (0.06) GG: 0.04 (0.24)	6.5
BovineHD1800014677	rs134833064	18	49839220	0.38	A/G	AA: 0.08 (0.06) GG: -0.28 (0.05)	6.0 <sup>2</sup>

<sup>1</sup> Minor Allele Frequency

<sup>2</sup> Suggestive association (FDR 0.20)

