Detection of candidate regions affecting bovine IgM natural antibodies in milk

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Background

• Specific Antibodies (SpAb)
  ➢ *Adaptive immunity*
    o Response to pathogen
    o Highly specific

• Natural Antibodies (NAb)
  ➢ *Innate immunity*
    o No previous exposure
    o 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)

- $\gamma \rightarrow 0.08 – 0.40$
- $\mu \rightarrow 0.39 – 0.45$
- $\lambda \rightarrow 0.30 – 0.55$

• IgA and IgM high genetic correlation
Background

Humoral response (Antibodies)

• SpAb
  o Mastitis  (Rupp et al. 2007, Thompson-Crispi et al. 2012)
  o Paratuberculosis  (Gonda et al. 2007, Minoza et al. 2010)
  o Nematodes  (Morris et al. 2002, Hayhurst et al. 2010)

• NAb
  o Productive life  (De Klerk et al. TBS)
  o Longer survival  (Sun et al. 2011)
  o 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-BTA-IgM-IgM
Materials and methods

Animals and phenotypes

• Dutch Milk Genomics Initiative (Stoop et al. 2008)
  o 1630 Holstein-Friesian cows
  o 379 herds
  o 66 to 263 DIM (166 avg.)
  o First calving

• NAb titers – Milk (Ploegaert et al. 2010)
  o Indirect ELISA
  o LTA-IgM
Materials and methods

GWAS

• Genotypes
  o Imputed 777K from 50K SNP chip
  o 576K

• Animal model (Schopen et al. 2011)
  o ASReml 4.1
  o Pedigree (4 generations)
  o Environmental effects
  o SNP as fixed effect
Results

Genomic regions (200kb)

• Two significant
  o BTA21, 71.2 – 71.6 Mb (4 SNPs)
  o BTA17, 72.9 – 73.3 Mb (2 SNPs)

• One suggestive
  o BTA18, 49.6 – 50.0 Mb (1 SNP)
LTA-IgM

FDR < 5%
FDR < 20%
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

FDR < 5%
FDR < 20%
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:

\[ y_{ijklmn} = \mu + \beta_1 \text{dim}_{ijklmn} + \beta_2 e^{-0.05 \text{dim}_{ijklmn}} + \beta_3 \text{ca}_{ijklmn} + \beta_4 \text{ca}_{ijklmn}^2 + \text{season}_k + \text{scodel}_l + \text{SNP}_m + \text{herd}_n + \text{animal}_o + e_{ijklmn} \]
Table 1. Lead SNP of each chromosome with suggestive or significant associations with LTA-IgM.

<table>
<thead>
<tr>
<th>SNP</th>
<th>rs ID</th>
<th>chr</th>
<th>Position</th>
<th>MAF 1</th>
<th>Major/minor allele</th>
<th>Genotype effect (SE)</th>
<th>-log10 P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>BovineHD2100020886</td>
<td>rs135338912</td>
<td>21</td>
<td>71482201</td>
<td>0.30</td>
<td>C/T</td>
<td>CC: -0.17 (0.05) TT: 0.34 (0.07)</td>
<td>6.9</td>
</tr>
<tr>
<td>BovineHD1700021382</td>
<td>rs133519711</td>
<td>17</td>
<td>73125915</td>
<td>0.10</td>
<td>A/G</td>
<td>AA: 0.35 (0.06) GG: 0.04 (0.24)</td>
<td>6.5</td>
</tr>
<tr>
<td>BovineHD1800014677</td>
<td>rs134833064</td>
<td>18</td>
<td>49839220</td>
<td>0.38</td>
<td>A/G</td>
<td>AA: 0.08 (0.06) GG: -0.28 (0.05)</td>
<td>6.0 2</td>
</tr>
</tbody>
</table>

1 Minor Allele Frequency
2 Suggestive association (FDR 0.20)