Unravelling the genetic background for endocrine fertility traits in dairy cows

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Background

- Declining fertility in dairy cows
- Classical traits for genetic improvement
  - Biased by farm management
  - Low heritability ($h^2 < 0.1$)
  - Low rate of genetic gain
  - Do not directly reflect cows own physiology
Endocrine fertility traits

CLA: Commencement of luteal activity

LA60: Luteal activity during first 60 DIM

PLA: Proportion of samples with luteal activity within 60 DIM

$$PLA = \frac{n1}{n1+n2}$$

Genome-wide association study (GWAS)

- Genomic information can aid selection to improve fertility

Aim

- Identify genomic regions (QTL) associated to endocrine fertility traits
- Fine map target regions using sequence variants
## Materials and methods

### Phenotypes
- 2447 Holstein cows
- 3643 lactations
- 14 commercial herds
- 4 experimental herds
- Progesterone levels measured every 2 days or twice a week

### Genotypes
- 80K commercial herds
- 50K experimental herds
- Imputation to 100K
- Quality control (QC)
- 84K SNP for GWAS after QC
Materials and methods

Statistical model

GWAS with 85K SNP
- Single-locus regression per SNP
- Linear mixed model plus random polygenic effect
- Random permanent environmental effect
- Fixed effects: herd-year-season, parity, calving age

Imputation target region to sequence

Fine-mapping with sequence variants
- Target QTL region
- Model as in GWAS
## Results

<table>
<thead>
<tr>
<th>Trait</th>
<th>n</th>
<th>Mean</th>
<th>SD</th>
<th>$h^2$</th>
<th>SE</th>
</tr>
</thead>
<tbody>
<tr>
<td>CLA (days)</td>
<td>3524</td>
<td>38.53</td>
<td>18.04</td>
<td>0.14</td>
<td>0.04</td>
</tr>
<tr>
<td>PLA (%)</td>
<td>3597</td>
<td>0.56</td>
<td>0.3</td>
<td>0.15</td>
<td>0.04</td>
</tr>
<tr>
<td>LA60 (0-1)</td>
<td>3597</td>
<td>0.87</td>
<td>0.33</td>
<td>0.09</td>
<td>0.03</td>
</tr>
</tbody>
</table>

- Range heritability 0.09 – 0.15
- Range repeatability 0.25 – 0.34
Results - GWAS endocrine fertility traits

- Strongest association chromosome 3 (BTA 3)
- Multiple trait association BTA 3
Results - Target QTL region on BTA 3

Top significant SNPs from GWAS on chromosome 3

<table>
<thead>
<tr>
<th>Trait</th>
<th>Position top SNP (bp)</th>
<th>MAF</th>
<th>-log_{10}(P –value)</th>
</tr>
</thead>
<tbody>
<tr>
<td>CLA</td>
<td>95,240,284</td>
<td>0.2</td>
<td>5.46</td>
</tr>
<tr>
<td>PLA</td>
<td>90,669,666</td>
<td>0.2</td>
<td>6.41</td>
</tr>
<tr>
<td>LA60</td>
<td>90,669,666</td>
<td>0.2</td>
<td>5.76</td>
</tr>
</tbody>
</table>

- Same top SNP for PLA and LA60
- Target region: 85.68 – 95.66 Mb
Results - Fine-mapping BTA 3 with sequence variants

- Fine mapping confirmed QTL region from GWAS
- QTL region narrowed to 2-3 Mb
## Results - Effect size

### Top significant SNPs from analysis with sequence

<table>
<thead>
<tr>
<th>Trait</th>
<th>Top SNP</th>
<th>-log(_{10}(P \text{ – value}))</th>
<th>Effect</th>
<th>SE</th>
</tr>
</thead>
<tbody>
<tr>
<td>CLA</td>
<td>Chr3:89795380</td>
<td>6.1</td>
<td>-0.22</td>
<td>0.04</td>
</tr>
<tr>
<td>PLA</td>
<td>Chr3:89360154</td>
<td>7.84</td>
<td>0.88</td>
<td>0.15</td>
</tr>
<tr>
<td>LA60</td>
<td>Chr3:89360154</td>
<td>7.17</td>
<td>0.83</td>
<td>0.15</td>
</tr>
</tbody>
</table>

- Possibility for marker-assisted selection strategies
- Genomic prediction strategies
Results - Fine-mapping BTA 3 with sequence variants

- CLA, PLA and LA60 are influenced by the same group of genes
# Results – Candidate genes

<table>
<thead>
<tr>
<th>Start</th>
<th>Stop</th>
<th>Gene</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>88373429</td>
<td>89715658</td>
<td>DAB1</td>
<td>Dab, reelin signal transducer, homolog 1 (Drosophila)</td>
</tr>
<tr>
<td>89742861</td>
<td>89786236</td>
<td>C8B</td>
<td>complement component 8, beta polypeptide</td>
</tr>
<tr>
<td>89758813</td>
<td>89779950</td>
<td>LOC104971750</td>
<td>uncharacterized LOC104971750</td>
</tr>
<tr>
<td>89797013</td>
<td>89869019</td>
<td>C8A</td>
<td>complement component 8, alpha polypeptide</td>
</tr>
<tr>
<td>89812210</td>
<td>89824630</td>
<td>LOC104971751</td>
<td>uncharacterized LOC104971751</td>
</tr>
<tr>
<td>89913524</td>
<td>90041725</td>
<td>C3H1orf168</td>
<td>chromosome 3 open reading frame, human C1orf168</td>
</tr>
<tr>
<td>90028764</td>
<td>90031862</td>
<td>LOC104971752</td>
<td>uncharacterized LOC104971752</td>
</tr>
<tr>
<td>90055299</td>
<td>90127206</td>
<td>PRKAA2</td>
<td>protein kinase, AMP-activated, alpha 2 catalytic subunit</td>
</tr>
<tr>
<td>90185284</td>
<td>90274552</td>
<td>PPAP2B</td>
<td>phosphatidic acid phosphatase type 2B</td>
</tr>
</tbody>
</table>
Conclusion

✓ Endocrine fertility traits (CLA, PLA and LA60) are associated to the same QTL region on chromosome 3 (BTA 3)
✓ Fine-mapping with sequence variants narrowed QTL region to 2-3 Mb
✓ CLA, PLA and LA60 are influenced by the same group of genes on BTA 3
Acknowledgements

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