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Unravelling the genetic background for endocrine fertility traits in dairy cows

Amabel Tenghe, *Aniek Bouwman, Erling Strandberg,*
Britt Berglund, and Roel Veerkamp

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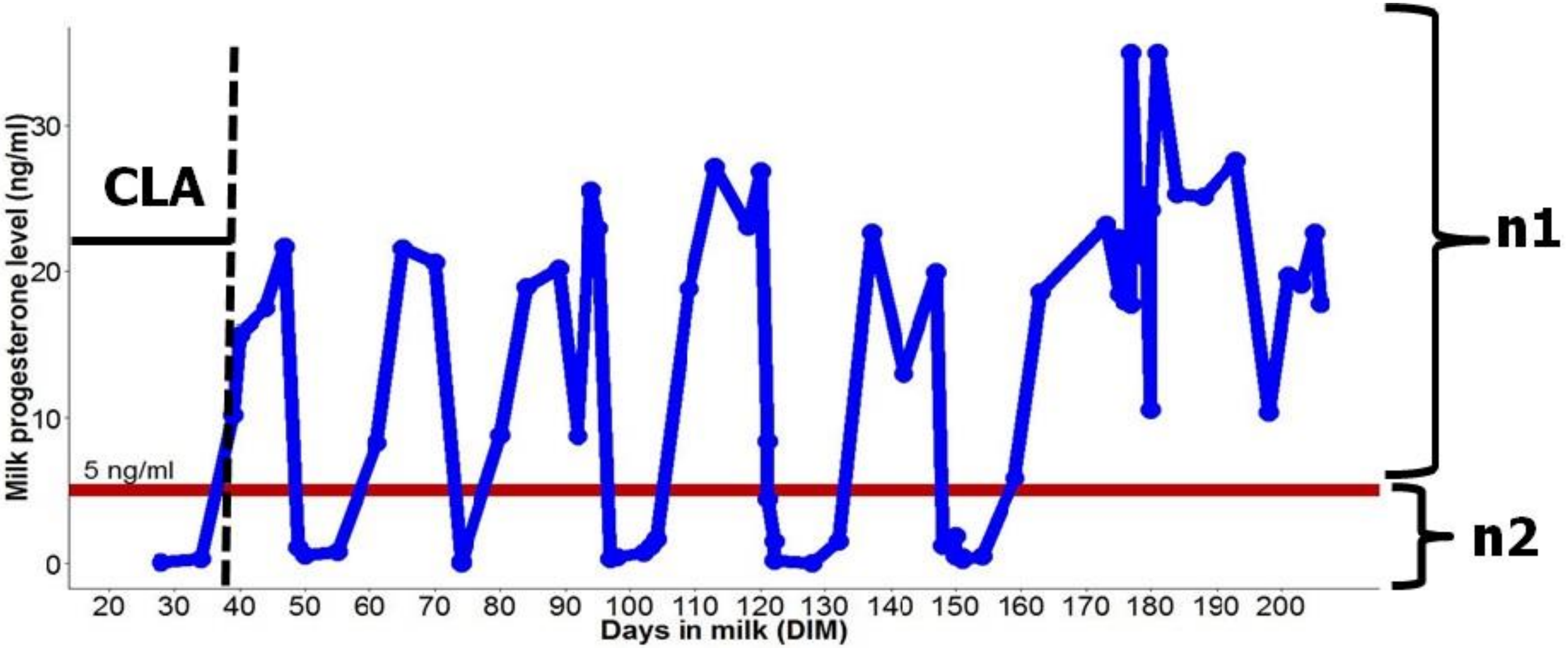
Background

- 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 = n1/(n1+n2)

Tenghe et al. 2014, JDS doi:10.3168/jds.2014-8732

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

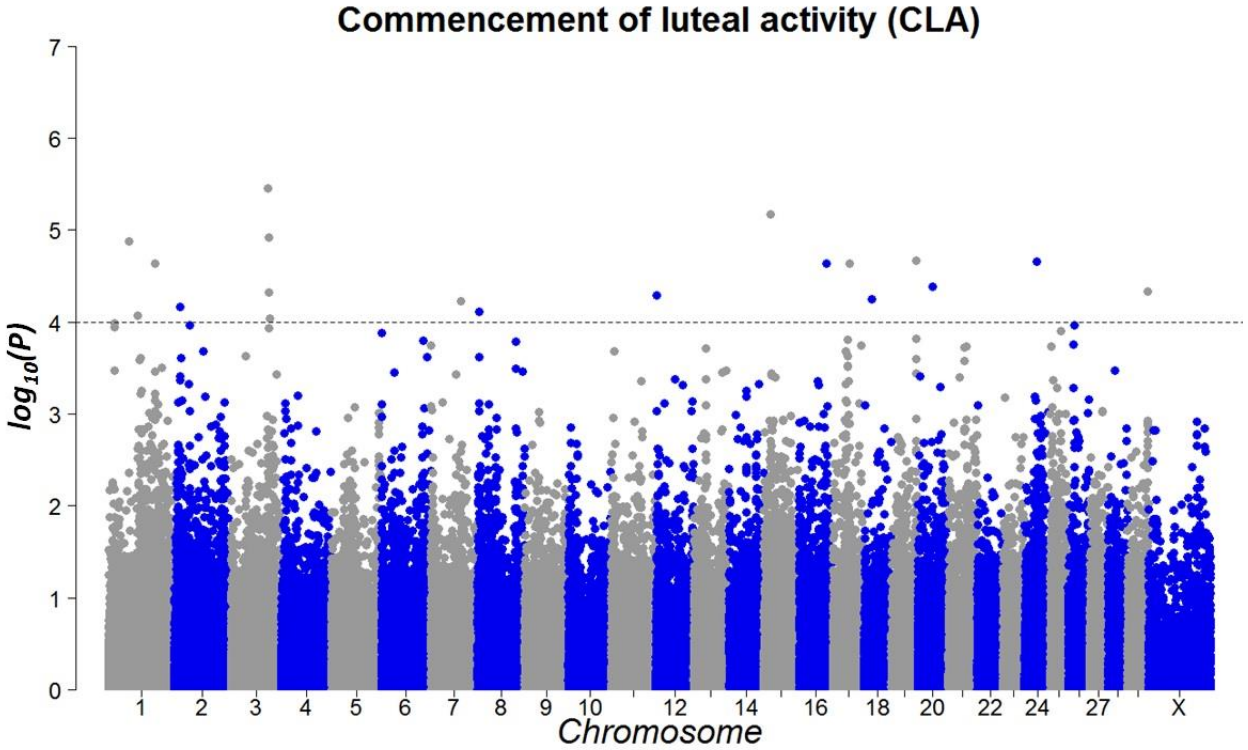
Results

Summary statistics and genetic parameters

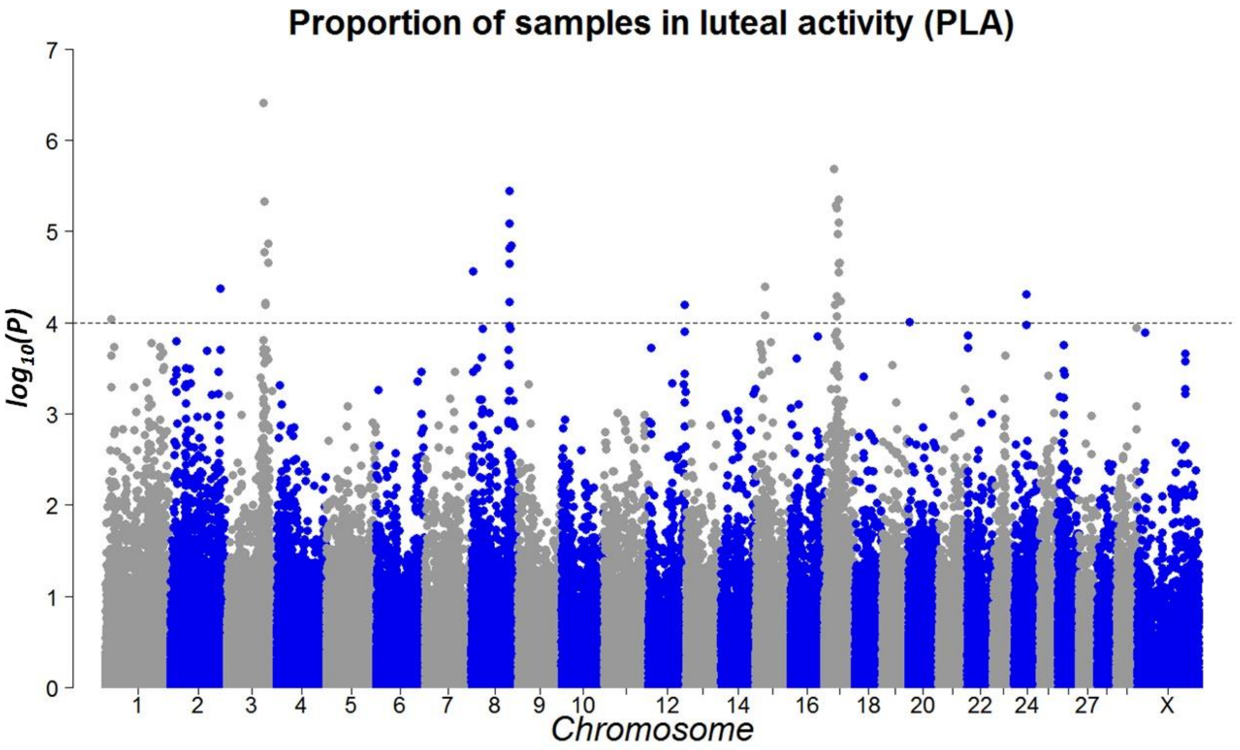
Trait	n	Mean	SD	h^2	SE
CLA (days)	3524	38.53	18.04	0.14	0.04
PLA (%)	3597	0.56	0.3	0.15	0.04
LA60 (0-1)	3597	0.87	0.33	0.09	0.03

- Range heritability 0.09 – 0.15
- Range repeatability 0.25 – 0.34

Results - GWAS endocrine fertility traits



Commencement of luteal activity (CLA)



Proportion of samples in luteal activity (PLA)

- Strongest association chromosome 3 (BTA 3)
- Multiple trait association BTA 3

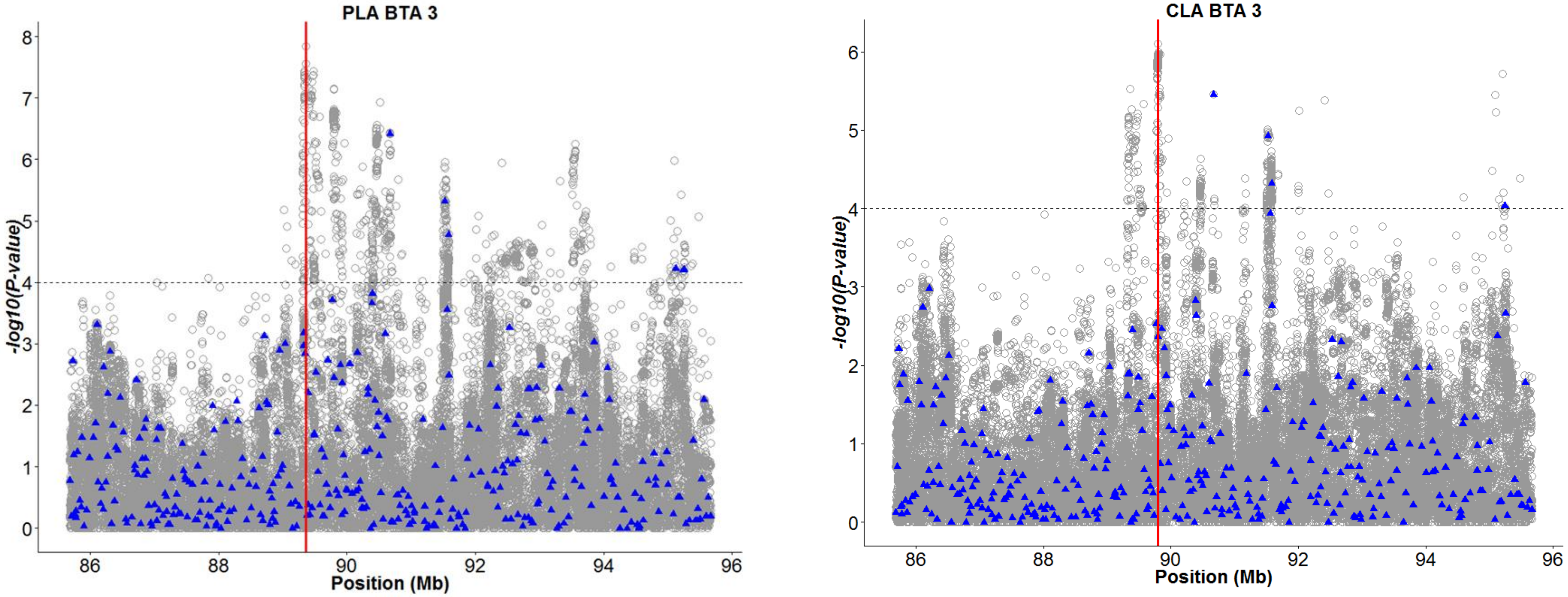
Results - Target QTL region on BTA 3

Top significant SNPs from GWAS on chromosome 3

Trait	Position top SNP (bp)	MAF	$-\log_{10}(P\text{ –value})$
CLA	95,240,284	0.2	5.46
PLA	90,669,666	0.2	6.41
LA60	90,669,666	0.2	5.76

- ❑ 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

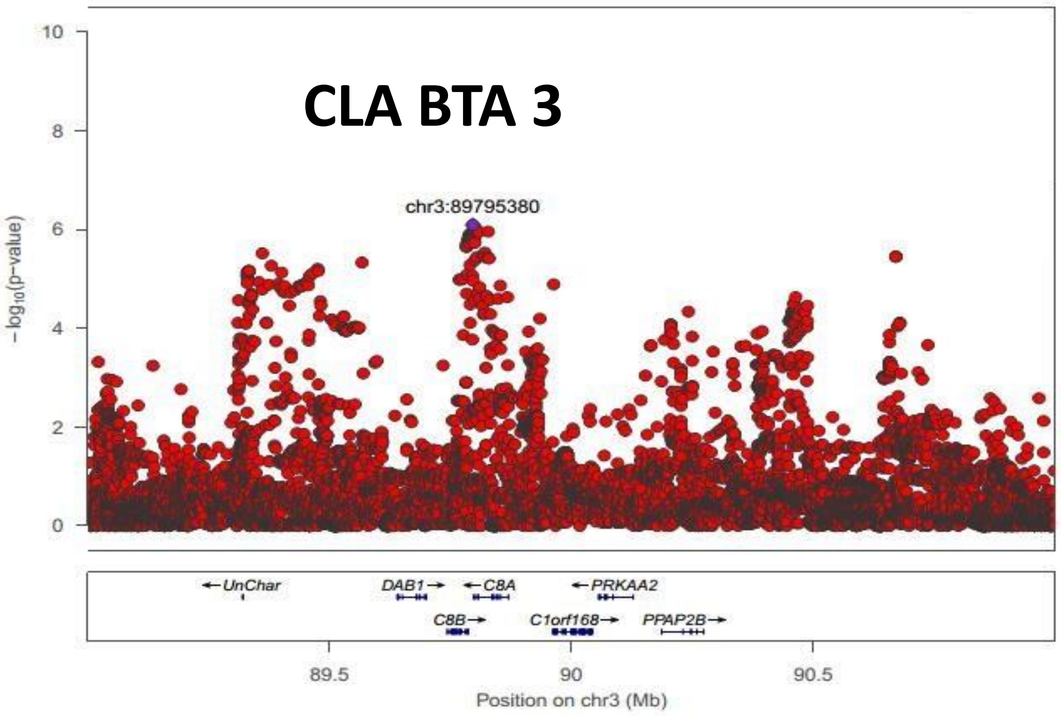
Results - Effect size

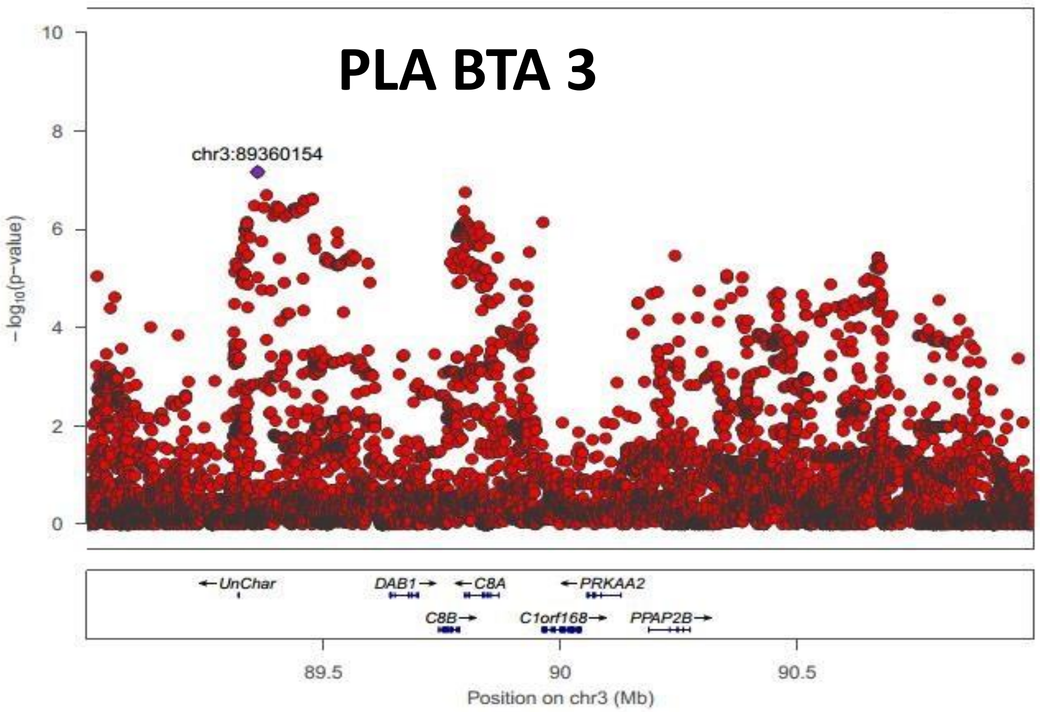
Top significant SNPs from analysis with sequence

Trait	Top SNP	$-\log_{10}(P - \text{value})$	Effect	SE
CLA	Chr3:89795380	6.1	-0.22	0.04
PLA	Chr3:89360154	7.84	0.88	0.15
LA60	Chr3:89360154	7.17	0.83	0.15

- 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

Start	Stop	Gene	Description
88373429	89715658	DAB1	Dab, reelin signal transducer, homolog 1 (Drosophila)
89742861	89786326	C8B	complement component 8, beta polypeptide
89758813	89779950	LOC104971750	uncharacterized LOC104971750
89797013	89869019	C8A	complement component 8, alpha polypeptide
89812210	89824630	LOC104971751	uncharacterized LOC104971751
89913524	90041725	C3H1orf168	chromosome 3 open reading frame, human C1orf168
90028764	90031662	LOC104971752	uncharacterized LOC104971752
90055299	90127206	PRKAA2	protein kinase, AMP-activated, alpha 2 catalytic subunit
90185284	90274552	PPAP2B	phosphatidic acid phosphatase type 2B

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

Data

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Lattec

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