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Pleiotropic effects in functional traits in cattle

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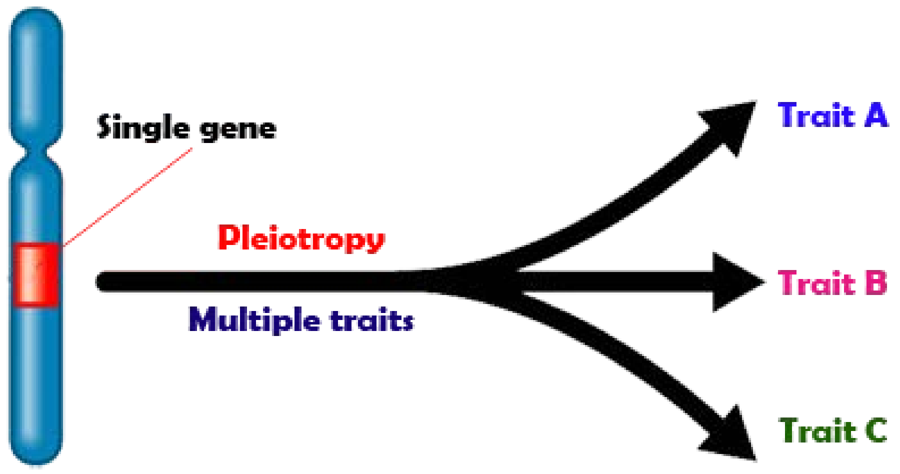
Introduction

- Pleiotropy: a single locus affects two or more phenotypic traits



- Positive and negative effects of pleiotropic genes on different traits
- Our area of interest: Functional traits

Aim

- Identify genomic regions with simultaneous effects for multiple functional traits in Fleckvieh cattle

- Identify possible pleiotropic genes in these regions

Materials and Methods

- Phenotypes: deregressed breeding values for
    - Calving ease
    - Stillbirth
    - Length of productive life
    - Fertility
- Genotypes:
    - 50K (v1 and v2) and HD SNP chips - 41,889 SNPs after merging and standard quality control
    - German and Austrian Fleckvieh cattle - 5,673 to 7,384 depending on the trait combination

Data acknowledgments

FLECKVIEH AUSTRIA

ZuchtData
EDV-DIENSTLEISTUNGEN GMBH

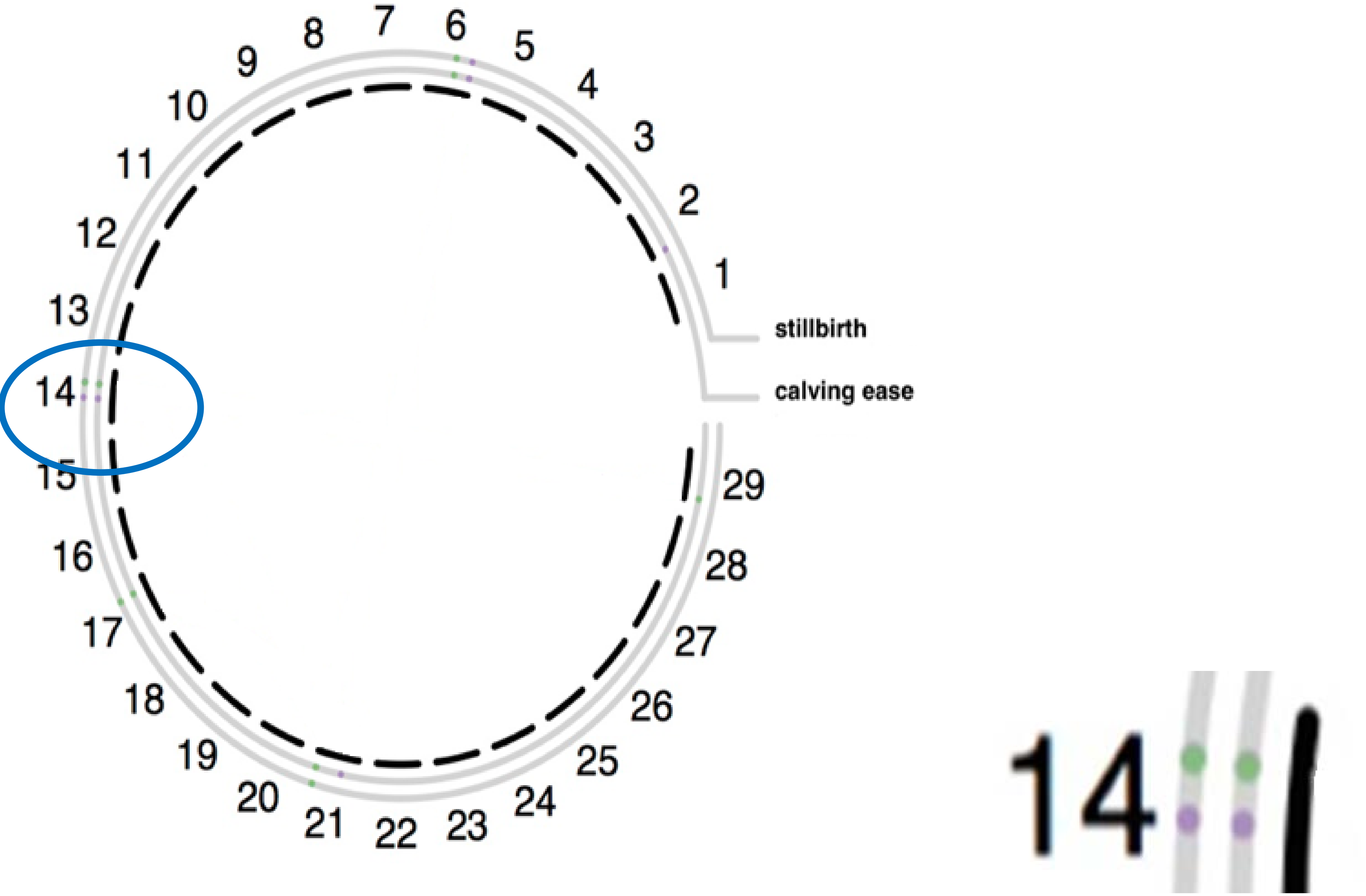
ASR
Arbeitsgemeinschaft
Süddeutscher Rinderzucht-
und Besamungsorganisationen e.V.

LfL
Bayerische Landesanstalt für Landwirtschaft

Materials and Methods

- Analysis approach
  - Singular value decomposition of traits - eigentraits (ET)
  - Two ET explaining the most variance selected
  - LD pruning and single variant scan to find 100 most influential loci
  - Scan of phenotype pairs with multivariate linear regression
    - Intercept, main effects and interaction term for each marker pair
    - The significant main effect coefficients for variant-to-phenotype influences for **both** traits denote pleiotropy

- Combined Analysis of Pleiotropy and Epistasis (CAPE) R package


7
6
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2
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stillbirth
calving ease
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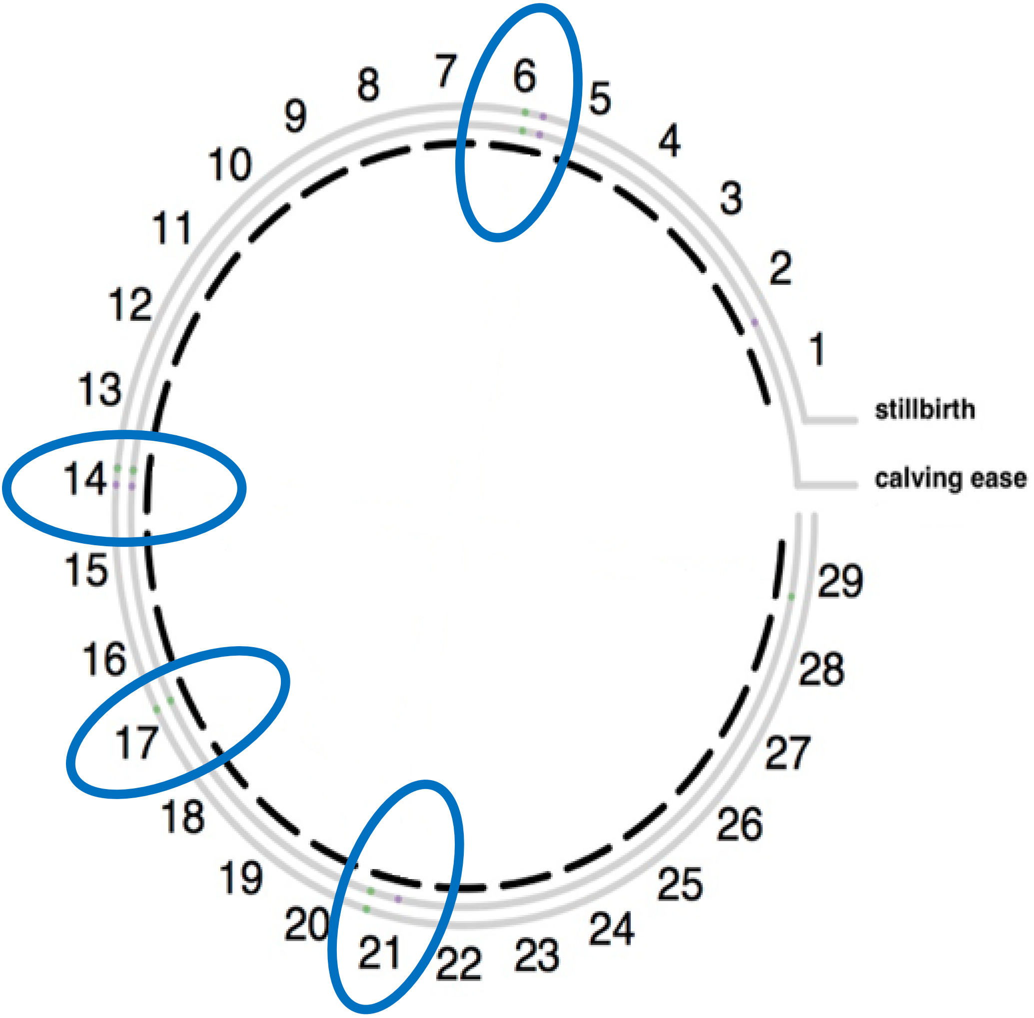
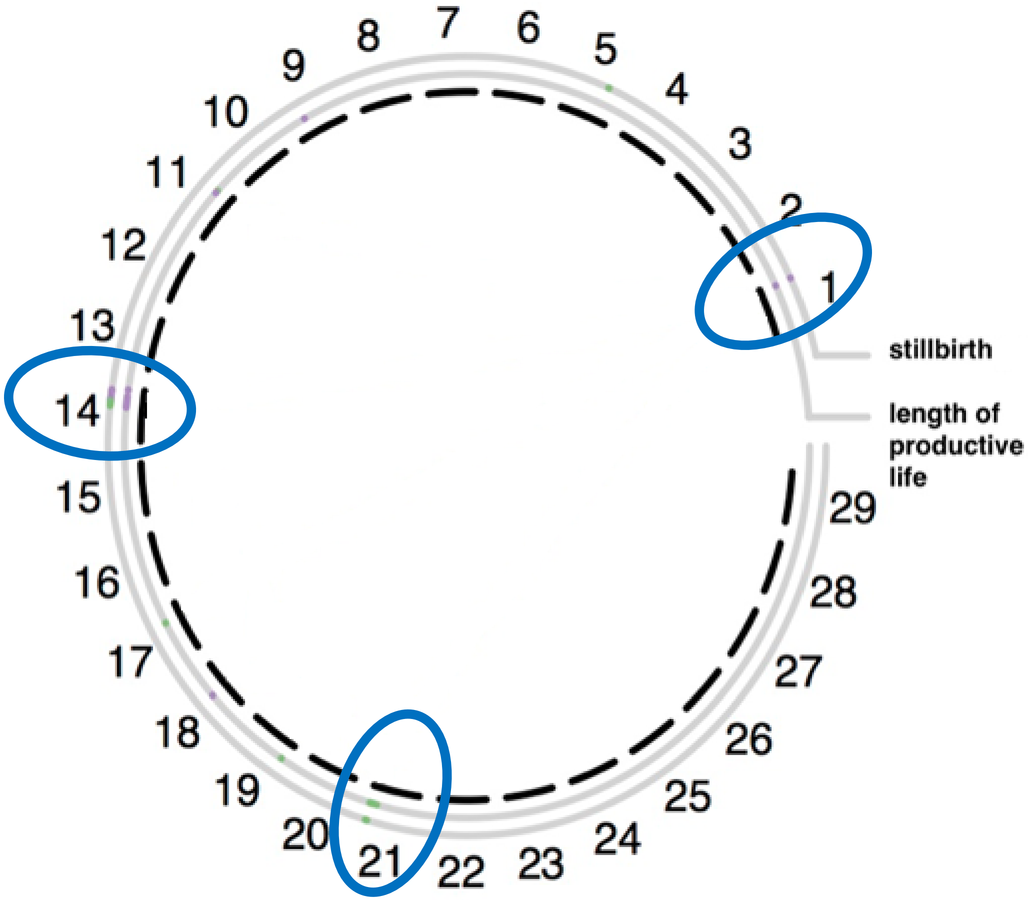
Stillbirth and calving ease



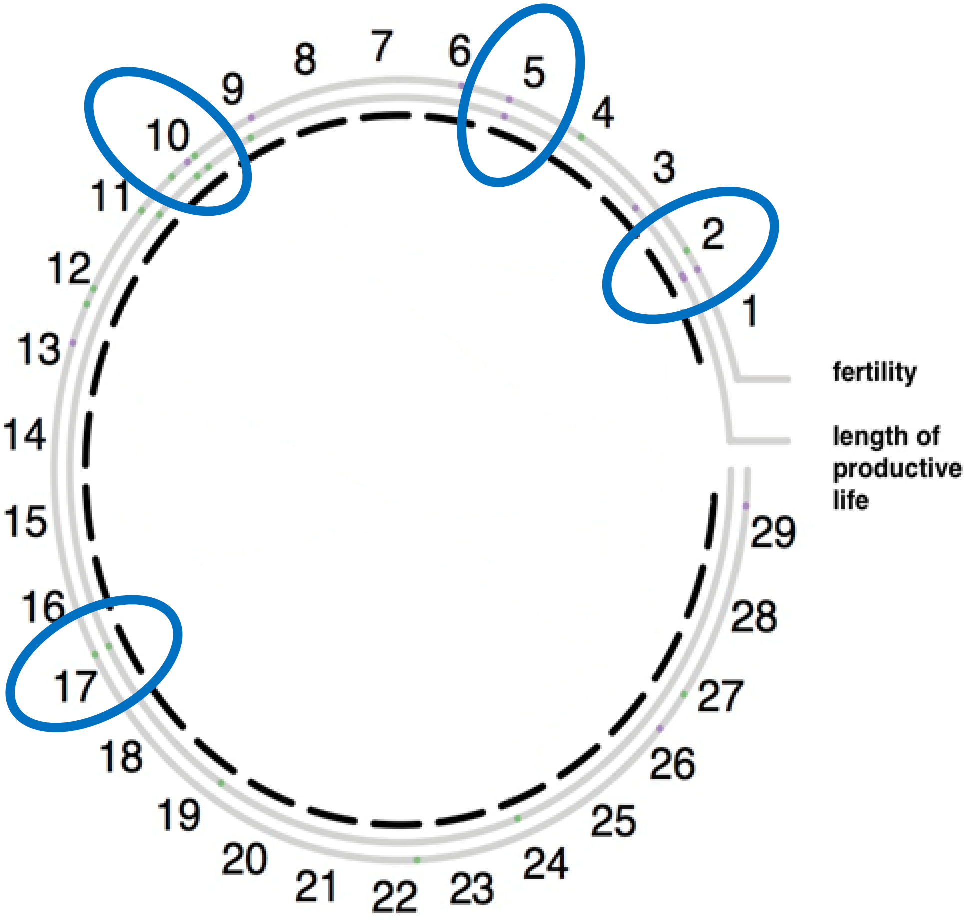
- BTA6: ~4.3 Mb (*QRFPR*, *NDNF*, *PRDM5*)
  ~47 Mb (*RBPJ*, *CCKAR*)
- BTA14: ~24 Mb (*RGS20*, *LYPLA1*, *MRPL15*, *SOX17*, *RP1*, *XKR4*)
- BTA17: ~17.5 Mb (*RNF150*, *TBC1D9*, *UCP1*, *ELMOD2*, *CLGN*)
- BTA21: ~2.5 Mb (*UBE3A*, *ATP10A*)

Stillbirth and longevity



- BTA1: ~150 Mb (*SIM2, HLCS*, *RIPPLY3*)
- BTA14: ~16 Mb (*TRIB1*)
  ~24.3 Mb (*XKR4, PLAG1*)
- BTA21: ~2.5 Mb (*UBE3A, ATP10A*)

Fertility and longevity



- BTA2: ~20.8 Mb (*HOXD1, HOXD3, HOXD4)*
- BTA5: ~98.5 Mb (*ETV6, BCL2L14, LRP6)*
- BTA10: ~51 Mb (*MYO1E*, *CCNB2*, *RNF111, SLTM*)
- BTA17: ~17.4 Mb (*RNF150*, *TBC1D9*, *UCP1*, *ELMOD2*, *CLGN*)

Details on interesting genes

- BTA14: *PLAG1* – early life body weight, growth and calving traits
  KCNQ3 – neural development and milk traits
  SOX17, RP1 and *XKR4* – growth and birth weight
  XKR4 – rump fat thickness and body condition

- BTA17*: CLGN* – spermatogenesis and fertility
  ELMOD2 – immune response
  UCP1 – thermoregulation

- BTA21: *UBE3A* – fetal growth

Cross check with GWAS

- GWAS runs to identify loci significantly associated with calving ease, stillbirth, fertility and length of productive life

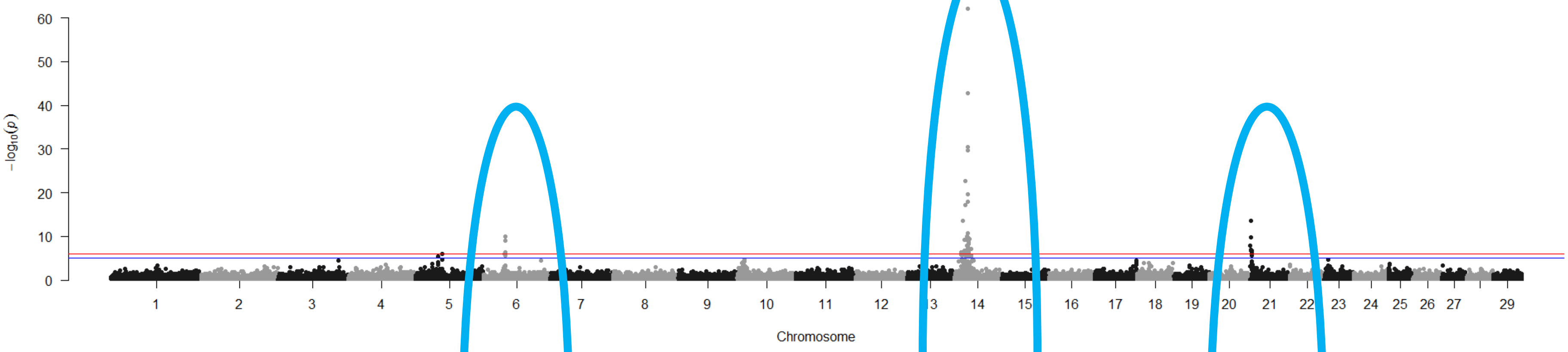
- Additional method to detect possible pleiotropic regions
    - Check if the same region appeared in different traits

- Results from univariate mixed linear model with Gemma

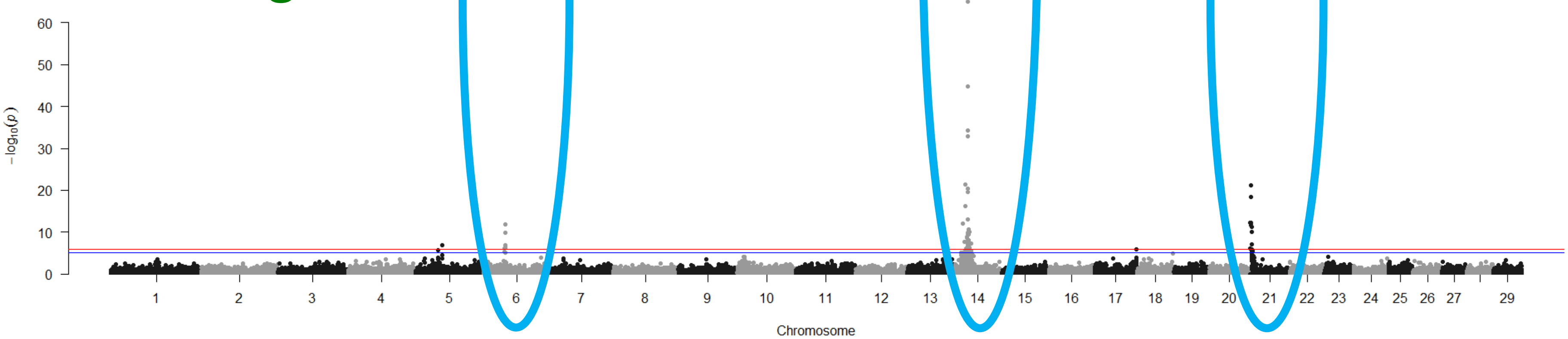
- The Bonferroni threshold is $-\log_{10}(p) = 5.9$ (red line) and an indicative threshold is $-\log_{10}(p) = 5$ (blue line)

Comparison of GWAS hits

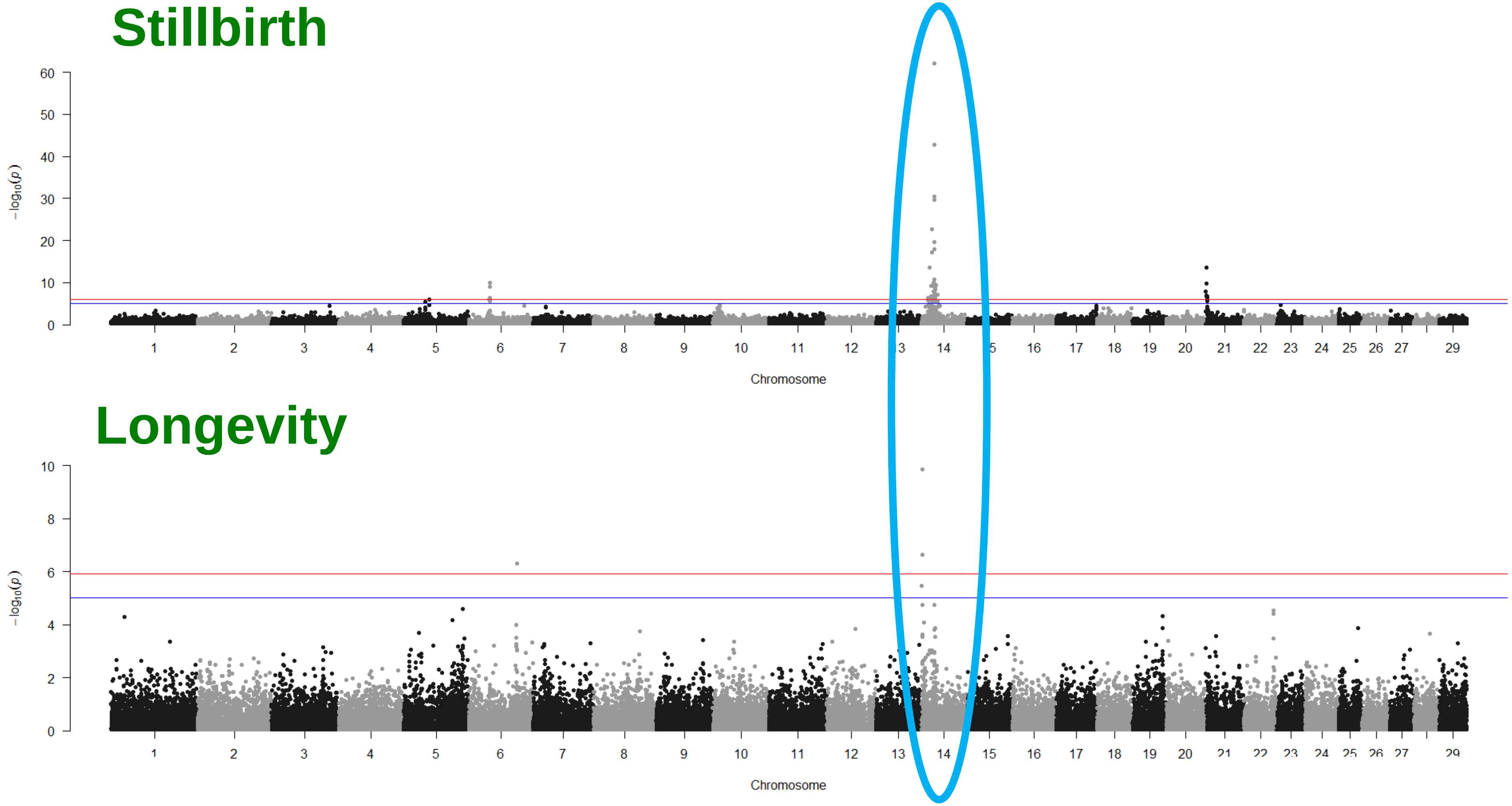
Stillbirth



Calving ease



Comparison of GWAS hits

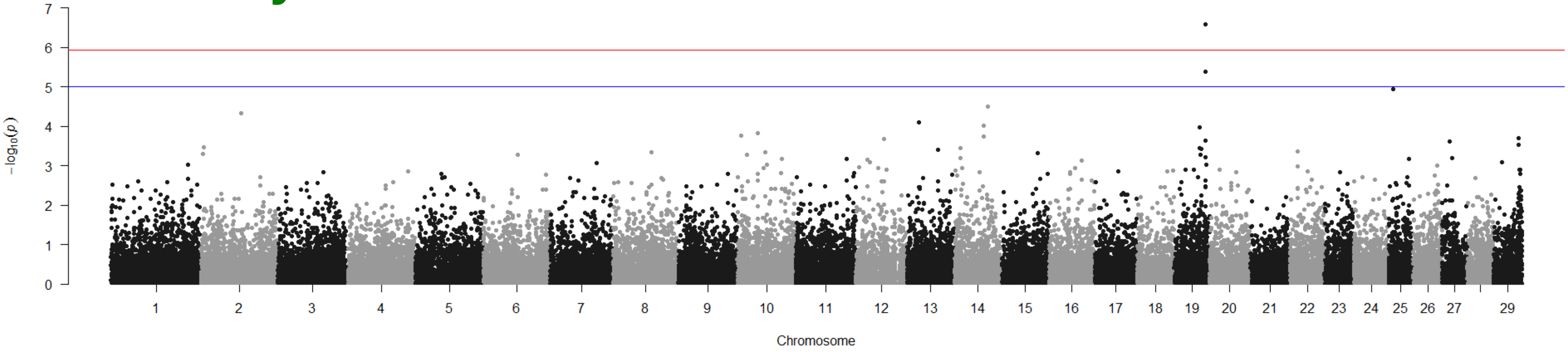


Stillbirth

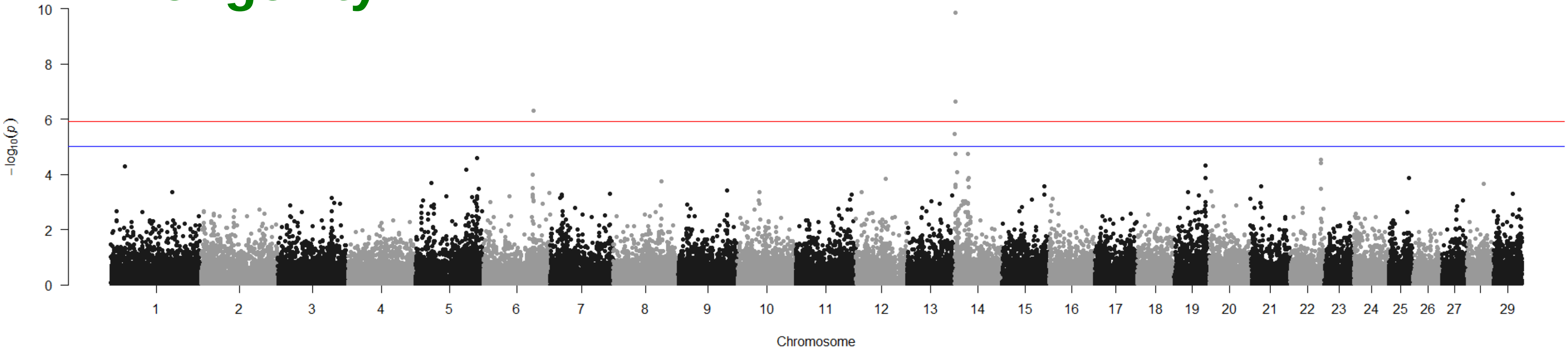
Longevity

Comparison of GWAS hits

Fertility



Longevity



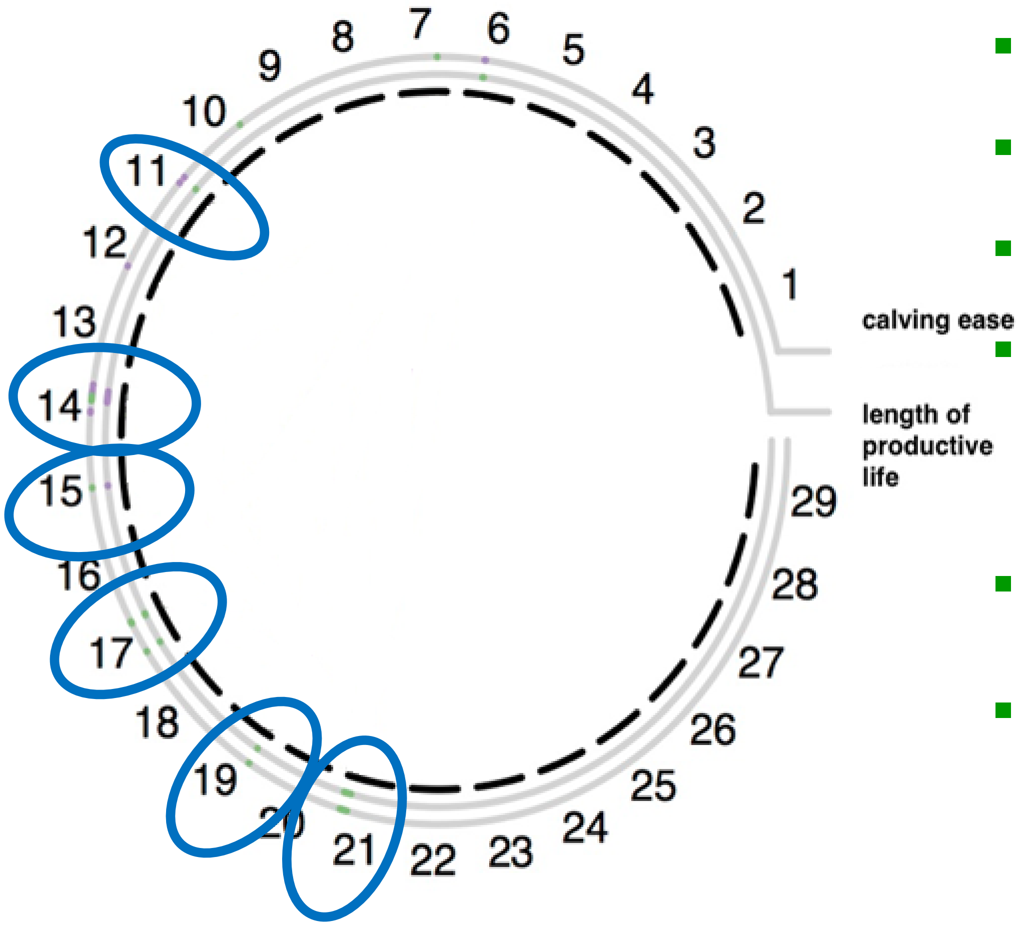
Conclusions

- Search for regions/genes responsible for pleiotropic interactions in complex traits in Fleckvieh cattle
- Strong evidence for pleiotropic effects on BTA6, 14, 17 and 21 for different trait combinations
- Different number of significant regions using different approaches to detect pleiotropy
- This study helps to explain the genetic architecture of functional traits in Fleckvieh cattle, and it provides useful information for breeding organisations

Thank you for your attention!

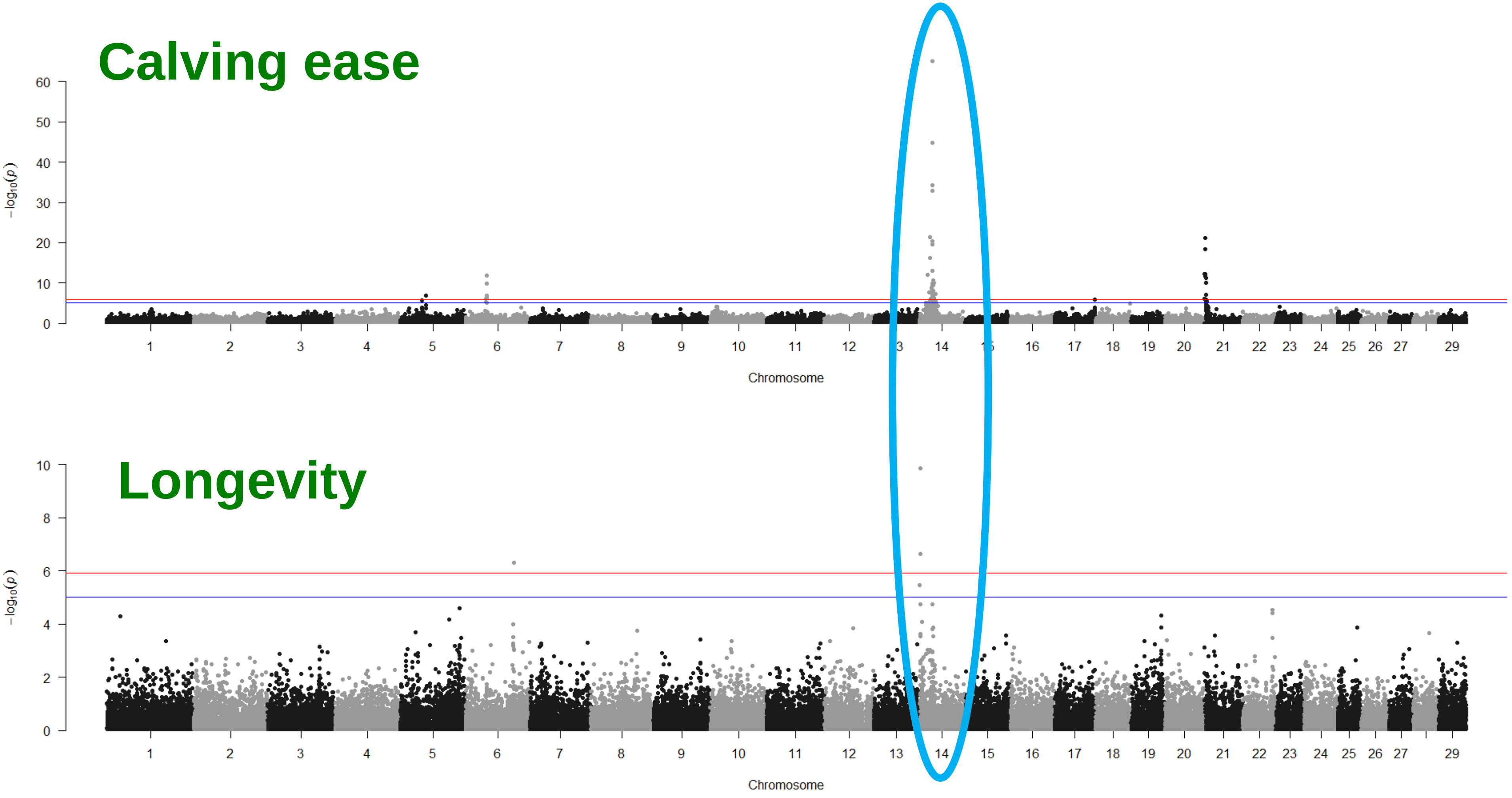
After end slides

Calving ease and longevity

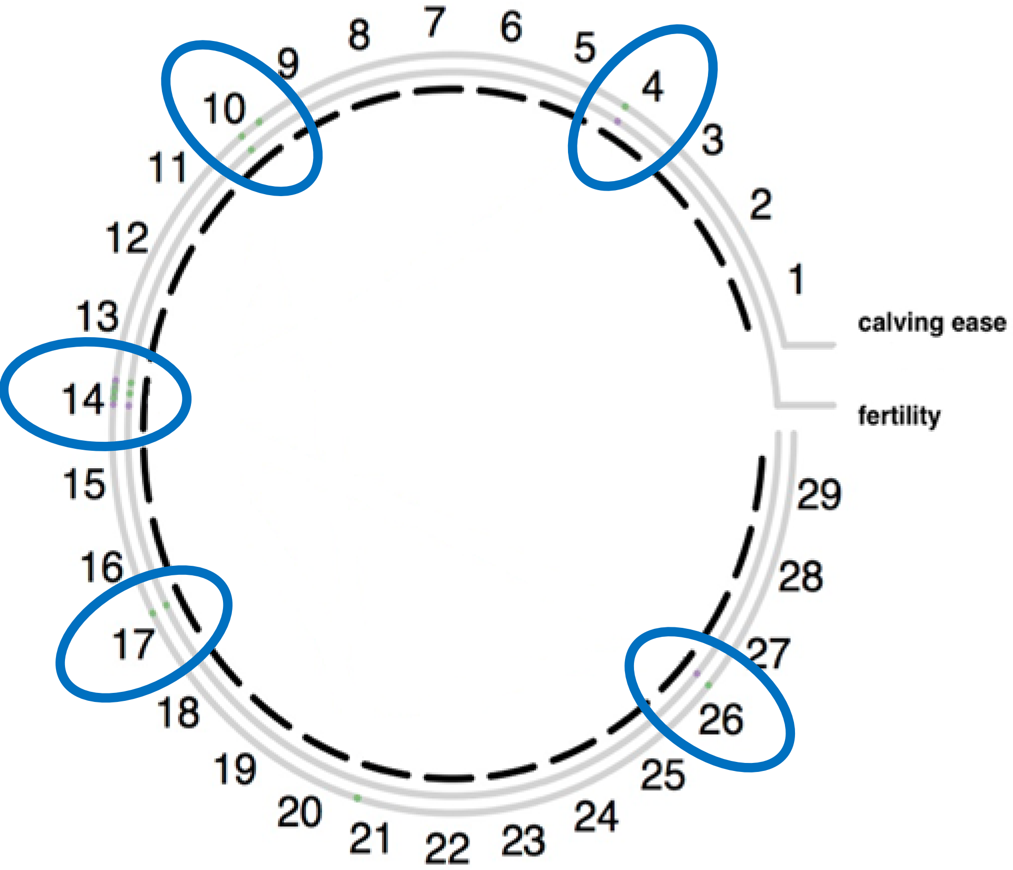


- BTA11: ~13.8 Mb (*FIGLA, ADD2, TGFA*)
- BTA14: ~24.3 Mb (*XKR4*)
- BTA15: ~45 Mb (*RIC3*, *TUB*, *NLRP10*)
- BTA17: ~17.5 Mb (*TBC1D9*, *UCP1*, *ELMOD2*, *CLGN*)
  ~ 64.5 Mb (ALDH2, CCD634)
- BTA19: ~56.8 Mb (*GRB2, MRPS7, GGA3 NUP85*)
- BTA21: ~2.5 Mb (*UBE3A*, *ATP10A*)
  ~5.5 Mb (*GABRG3, VIMP, LRRK1*)
  ~10.8 Mb (*NR2F2*)

Comparison of GWAS hits



Calving ease and fertility

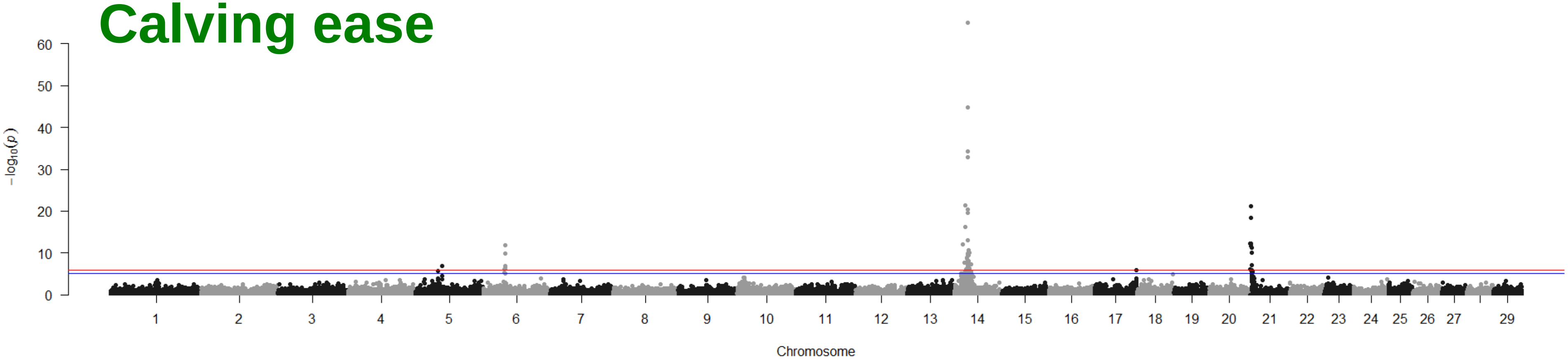


- BTA4: ~94.7 Mb (*UBE2H, KLHDC10, SSMEM1, CPA4, CPA5, CPA1, CEP41*)
- BTA10: ~56.3 Mb (*UNC13C*)
- BTA14: ~9.8 Mb (*KCNQ3, LRRC6*)

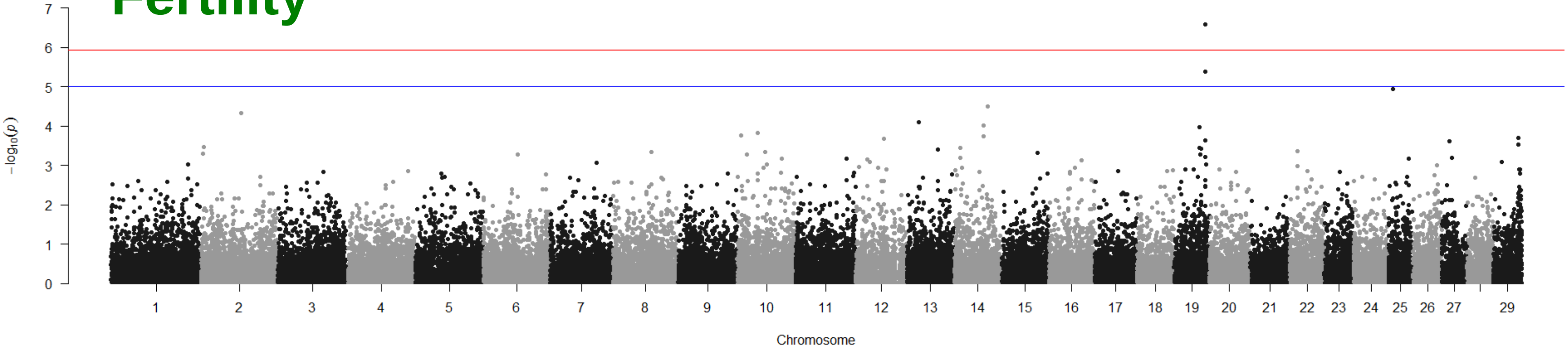
  ~47.5 Mb (*NOV*, *MAL2*, *SAMD12*)
- BTA17: ~17.5 Mb (*RNF150, TBC1D9, UCP1, ELMOD2, CLGN, SCOC*)
- BTA26: no genes

Comparison of GWAS hits

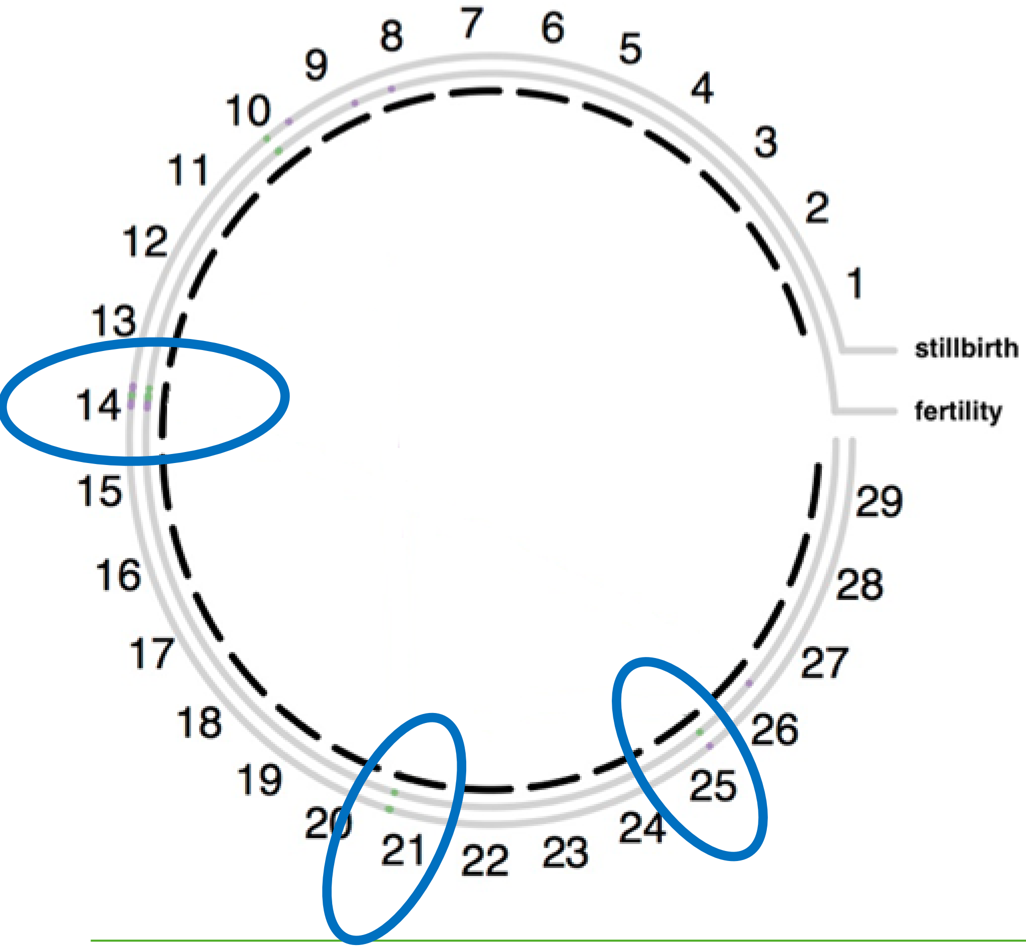
Calving ease



Fertility



Stillbirth and fertility



- BTA14: ~9.8 Mb (*KCNQ3, LRRC6*)

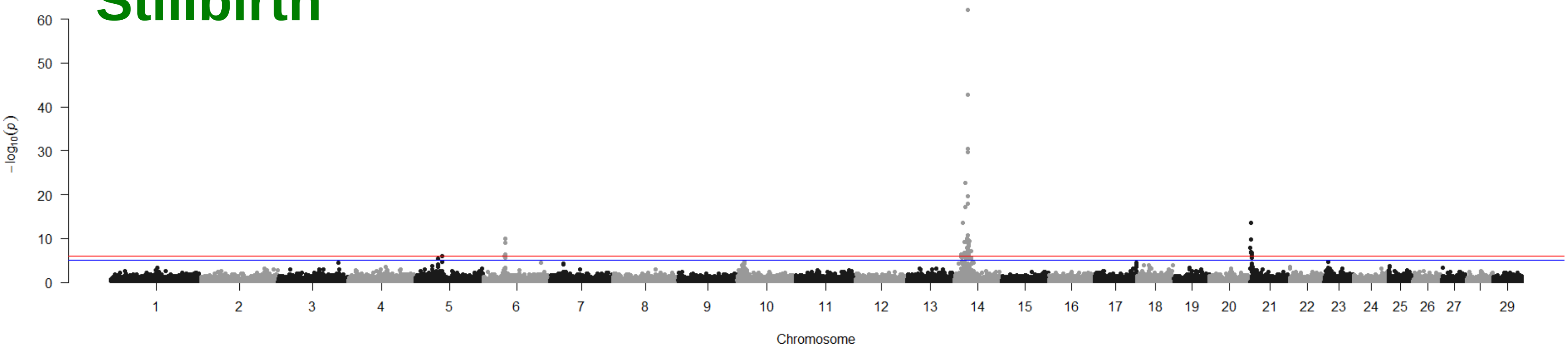
  ~24 Mb (*RGS20, LYPLA1, MRPL15, SOX17, RP1, XKR4*)

  ~36 Mb (*PRDM14, NCOA2, TRAM1, LACTB2, XKR9*)

- BTA21 and 25 no genes

Comparison of GWAS hits

Stillbirth



Fertility