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
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
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)
- BTA21: ~2.5 Mb (UBE3A, ATP10A)
- ~24.3 Mb (XKR4, PLAG1)
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

Longevity
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