Identifying genetic loci influencing body weight in the endangered dual-purpose German Black Pied (DSN) cattle breed

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Deutsches Schwarzbuntes Niederungsrind (DSN)

In comparison to Holstein

- Endangered dual-purpose breed (~2.500 herdbook cows)
- Lower milk yield (305-day yield: 7,000-8,000 kg)
- Higher milk fat (4.3%) and protein (3.7%) content
- Good fertility, robustness

To preserve DSN

- Minimize inbreeding and maintain diversity [1]
- Breeding goals:
  - Maintain dual-purpose character
  - Improve milk yield and good milk fat and protein content [2, 3]
  - **Maintain high muscularity**

    → **Find markers associated with body weight and body weight gain**

[1] Neumann et al., 2023, *Frontiers in Genetics*
[2] Korkuć et al., 2021, *Frontiers in Genetics*
[3] Korkuć et al., 2023, *Genes*

Genotypes & traits

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POPULATION

- **669 DSN bulls** from one farm in Brandenburg
  - → 396 from DSN200K chip [1]
  - → 273 from EuroG MD chip
- Imputation to sequence level using 304 sequenced DSN

  Biallelic variants
  MAF ≥ 5%
  SNP call rate ≥ 90%
- **11.820.219 sequence variants**

[1] Neumann et al., 2022, *BMC Genomics*

TRAITS

- Single weightings (HERDE software)
  - **Body weight (BW)**
    - BW_{0d} (ø 0 days)
    - BW_{3w} (ø 3 weeks)
    - BW_{7m} (ø 7 months)
    - BW_{18m} (ø 18 months)
  - **Body weight gain (BWG)**
    - $BWG_{0d\text{-}3w}$ = BW_{3w} - BW_{0d}
    - $BWG_{0d\text{-}7m}$
    - $BWG_{3w\text{-}7m}$
    - $BWG_{0d\text{-}18m}$
    - $BWG_{3w\text{-}18m}$
    - $BWG_{7m\text{-}18m}$

Genome-wide association study

MODEL

population stratification, birth season, slaughter season, genotype

trait ← $\boldsymbol{Y} = \boldsymbol{ps} + \boldsymbol{by}^* + \boldsymbol{bs}^* + \boldsymbol{sy}^* + \boldsymbol{ss}^* + \boldsymbol{ag}^* + \mathbf{gt} + \boldsymbol{e}$

birth year, slaughter year, age, error

* Best-fit models were estimated based on Akaike information criterion using R package AICcmodavg

SIGNIFICANCE

After correction for inflation factor λ=1.2 and Bonferroni with 423,453 independet variants ($r^2 \leq 0.6$)

Suggestive associations: $p < 0.1$ → $-\log_{10}(p) = 6.6$

Significant associations: $p < 0.05$ → $-\log_{10}(p) = 6.9$

ANNOTATION

Genes (Ensembl release 110)

Impact of variants using VEP

Gene ontology enrichment analysis with g:Profiler

Comparison to cattleQTLdb (release 54)

11 QTLs on 6 chromosomes

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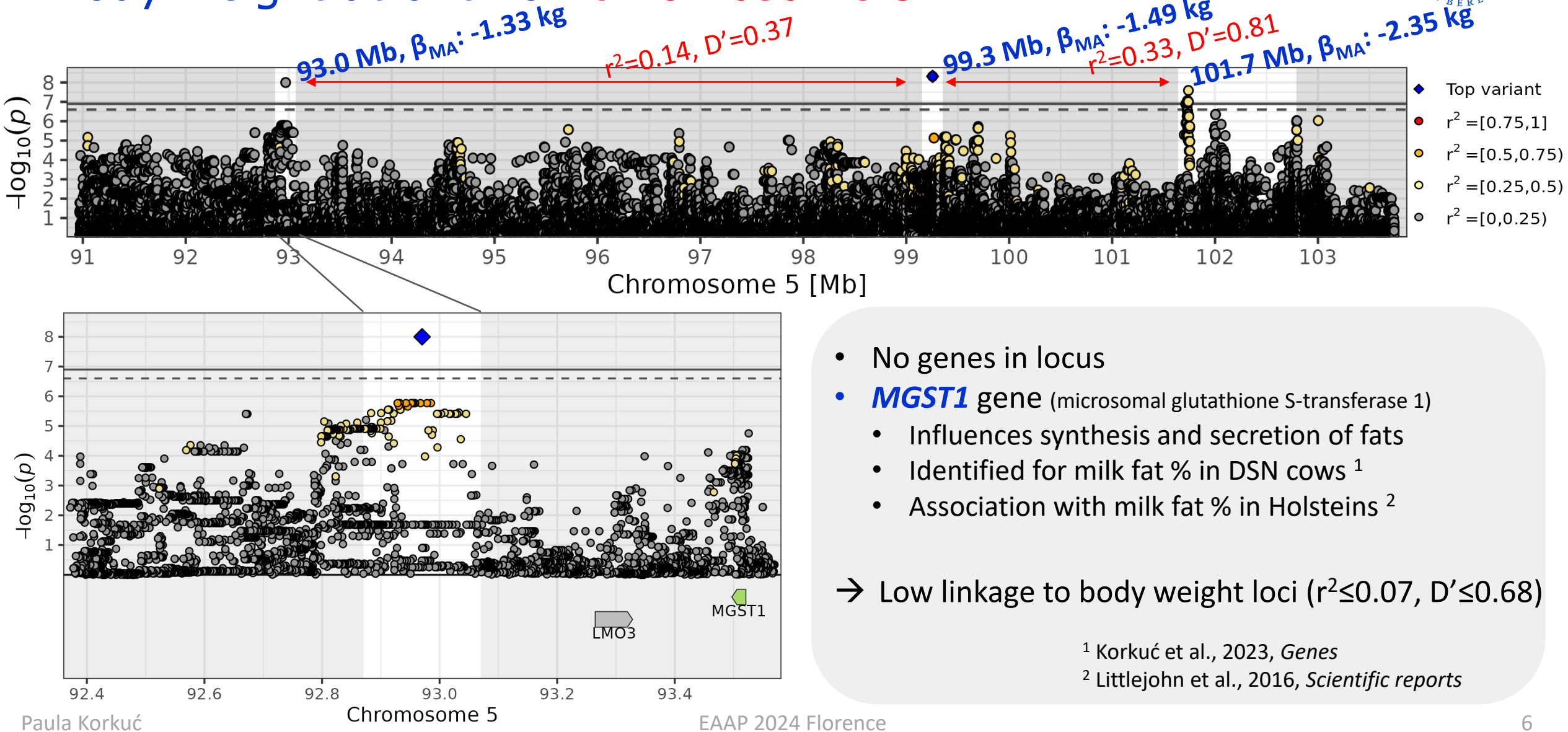
- 127 variants above suggestive threshold grouped into 11 QTLs → **8 significant QTLs**
- QTLs defined with 1.5 LOD drop within 2 Mb

Trait	# SNPs	# QTLs	Chr 2	Chr 3	Chr 5	Chr 10	Chr 16	Chr 18
BW_{0d}	82	5	58 Mb		**93, 99, 102 Mb**			**43 Mb**
BW_{3w}	8	3		**93 Mb**		52 Mb	**14 Mb**	
BW_{7m}	37	3		**27 Mb**, 44 Mb		**49 Mb**		
BW_{18m}								
BWG_{0d-3w}								
BWG_{0d-7m}	11	1				**49 Mb**		
BWG_{3w-7m}								
BWG_{0d-18m}								
BWG_{3w-18m}								
BWG_{7m-18m}								

Body weight at birth on chromosome 5

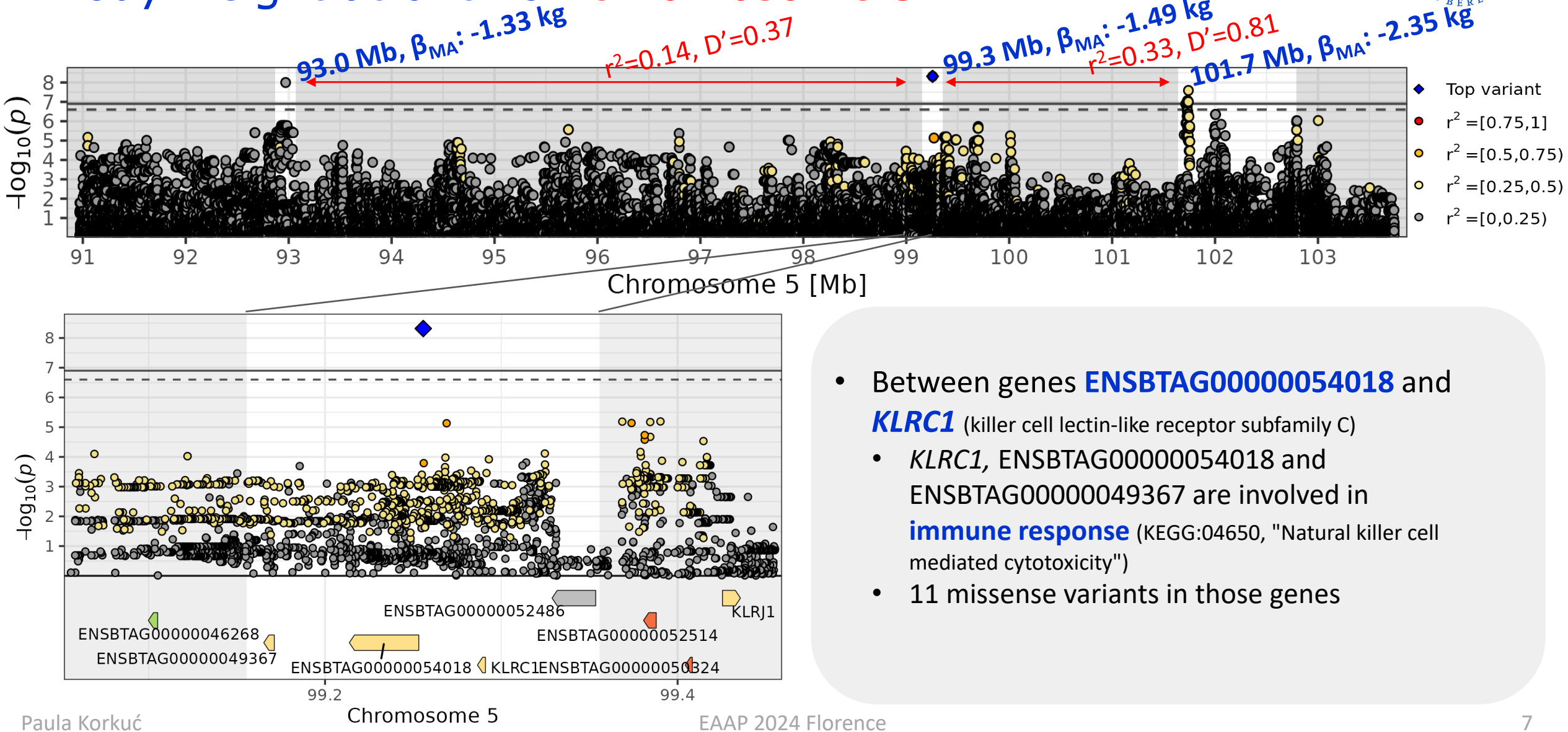


- No genes in locus
- ***MGST1*** gene (microsomal glutathione S-transferase 1)
  - Influences synthesis and secretion of fats
  - Identified for milk fat % in DSN cows [1]
  - Association with milk fat % in Holsteins [2]

→ Low linkage to body weight loci ($r^2 \leq 0.07$, $D' \leq 0.68$)

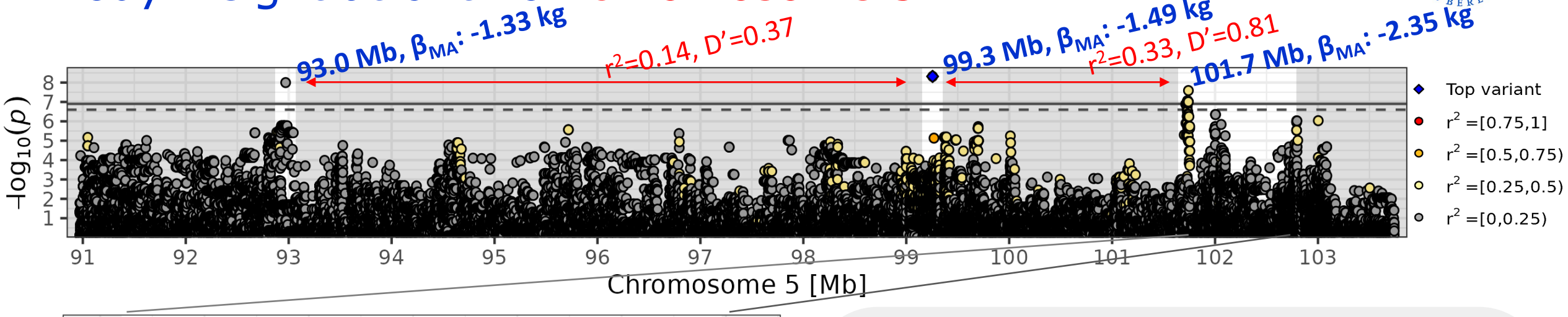
[1] Korkuć et al., 2023, *Genes*
[2] Littlejohn et al., 2016, *Scientific reports*

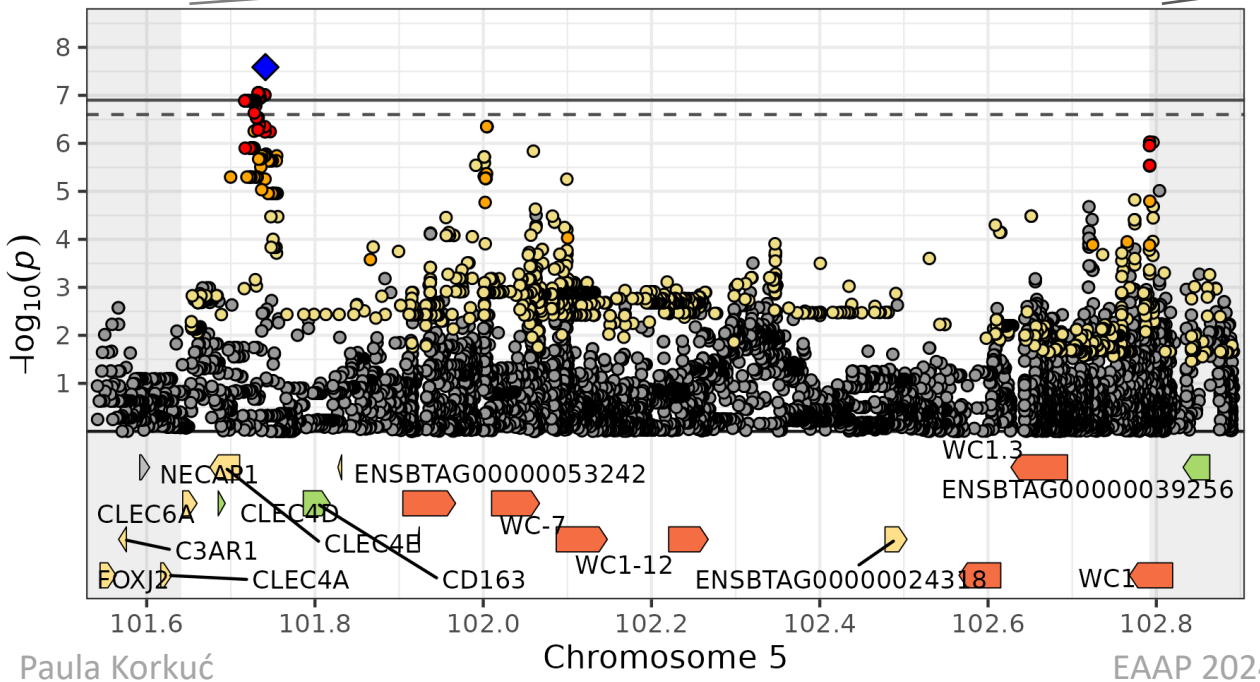
Body weight at birth on chromosome 5



- Between genes **ENSBTAG00000054018** and ***KLRC1*** (killer cell lectin-like receptor subfamily C)
  - *KLRC1,* ENSBTAG00000054018 and ENSBTAG00000049367 are involved in **immune response** (KEGG:04650, "Natural killer cell mediated cytotoxicity")
  - 11 missense variants in those genes

Body weight at birth on chromosome 5

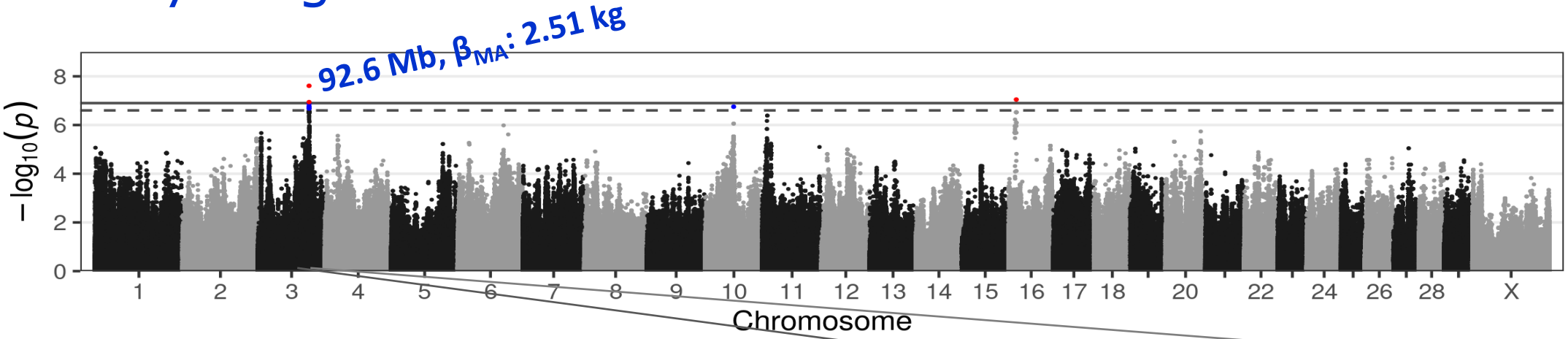




- Between ***CLEC4E*** (C-type lectin domain family 4 member E) and ***CD163*** (CD163 molecule)
  - ***CLEC…*** genes involved in **immune response**
  - Antifungal innate immune response (GO:0061760), defense response (GO:0006952), T cell activation involved in immune response (GO:0002286)
- Associated to "Length of productive life" in Holstein[1] and "Marbling score" in Hanwoo[2]

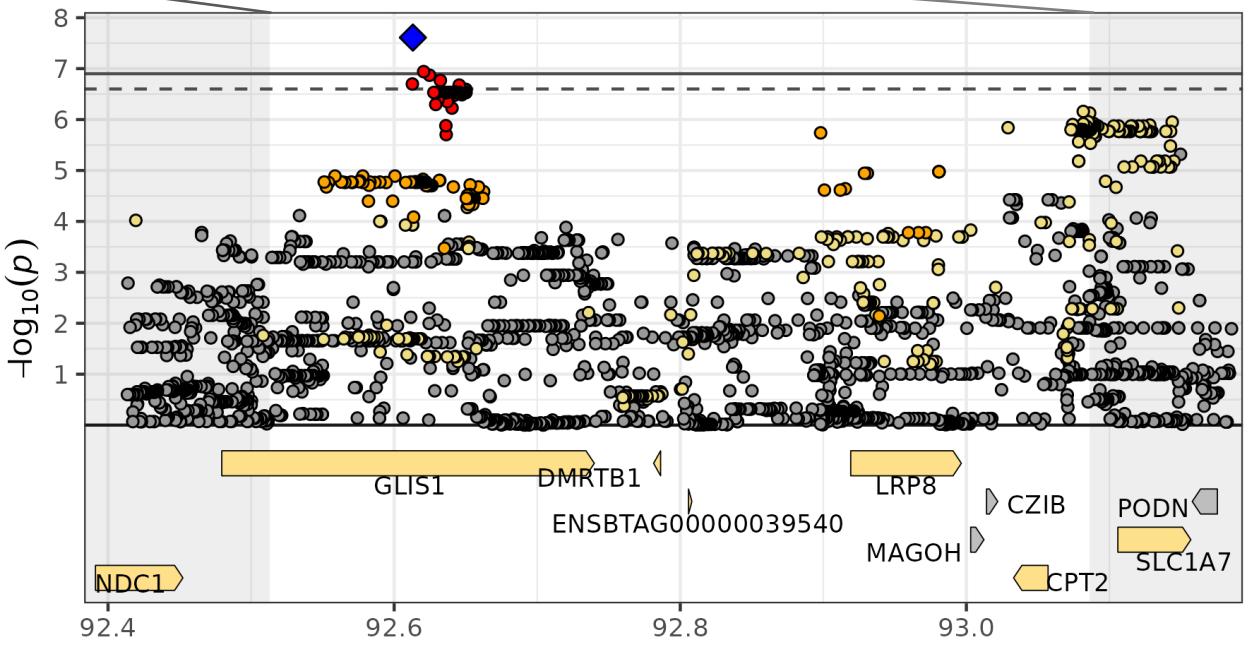
[1] Cole et al., 2012, *BMC Genomics,* [2] Li et al., 2020, *Asian-Austr. J Anim Sci.*

Body weight at 3 weeks on chromosome 3

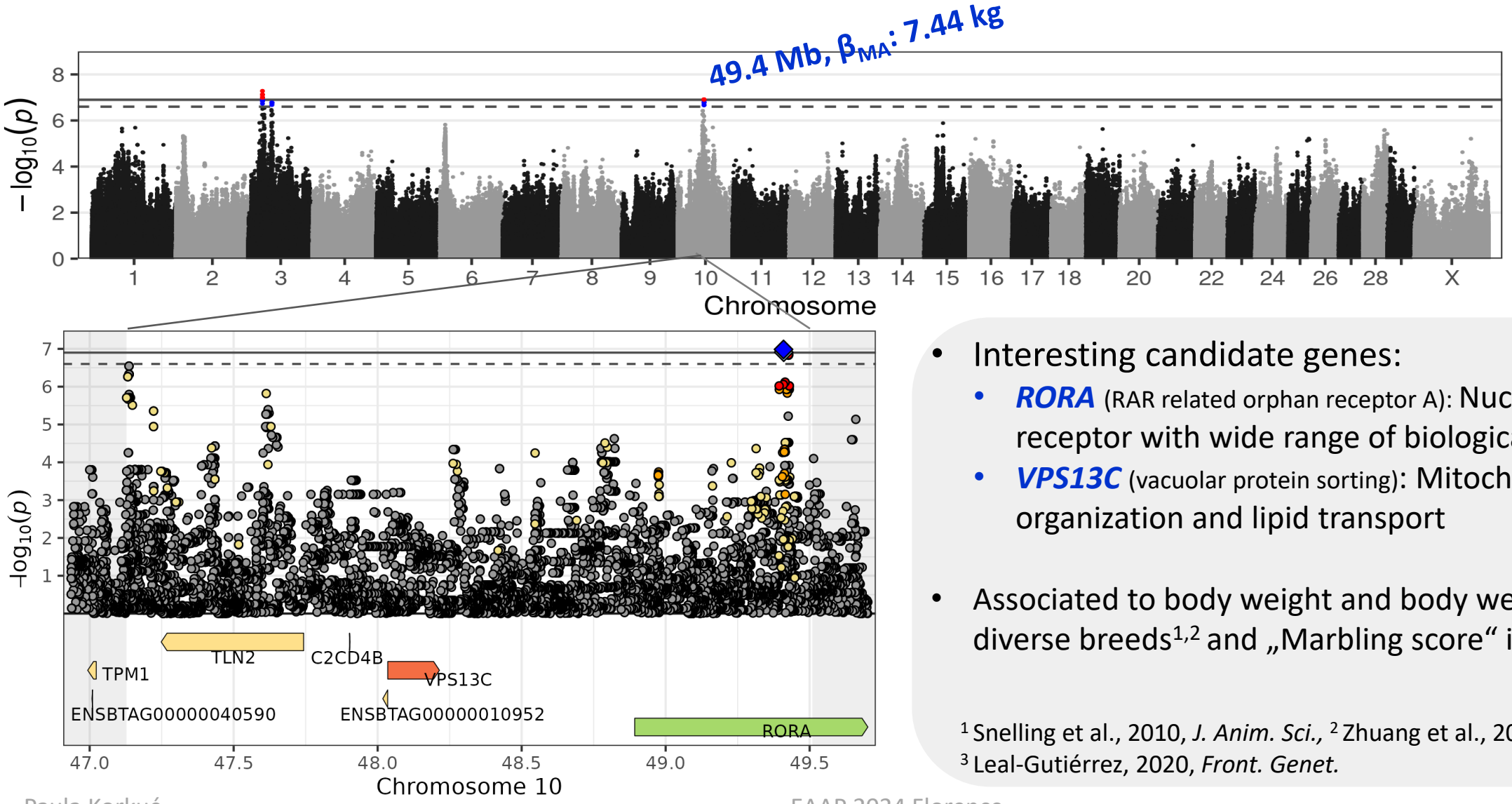


- Interesting candidate genes:
  - ***GLIS1*** (GLIS family zinc finger 1): TF regulating gene expression during **cell differentiation**
  - ***LRP8*** (LDL receptor related protein 8): Signal transduction, lysosomal degradation, migration of neurons
- Associated to "Length of productive life" in Holstein[1]

[1] Cole et al., 2012, *BMC Genomics*



Body weight at 7 months on chromosome 10



Locus was also associated with $BWG_{0d\text{-}7m}$

- Interesting candidate genes:
  - ***RORA*** (RAR related orphan receptor A): Nuclear hormone receptor with wide range of biological processes
  - ***VPS13C*** (vacuolar protein sorting): Mitochondrion organization and lipid transport
- Associated to body weight and body weight gain in diverse breeds[1,2] and „Marbling score“ in Angus[3]

[1] Snelling et al., 2010, *J. Anim. Sci.,* [2] Zhuang et al., 2020, *Genes*
[3] Leal-Gutiérrez, 2020, *Front. Genet.*

Summary

New Loci

- Identification of **11 QTLs for body weight and body weight gain** despite the relatively small sample size
- **Most loci for growth not linked to milk production loci**, except minimal linkage for loci on chromosome 5

Candidate Genes

- ***KLRC1*** and **C-type lectin family** genes suggest potential interplay between growth and health
- ***GLIS1*** directly influences tissue formation and growth
- ***RORA*** and other genes (not shown) may affect growth and development through their roles in metabolic processes, cellular signaling and nutrient transport

Conclusions

- Knowledge of growth and milk loci can help to **maintain dual-purpose character**
- **Selection for favored alleles** can improve e.g. body weight at birth (caution to birth difficulties)
- Challenge to select for favorable alleles while **maintaining diversity and avoiding inbreeding**

Thank you for your attention!

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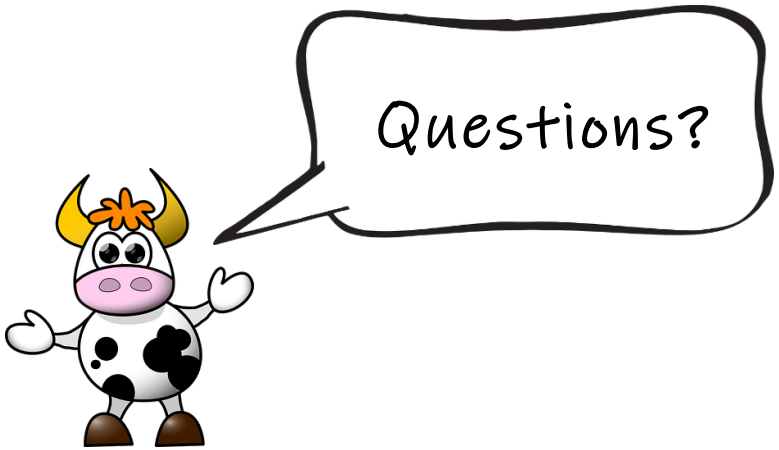

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