Across-breed analysis of genome-wide association studies for stature and mammary gland morphology in cattle reveals pleiotropic effects of the Friesian POLLED haplotype

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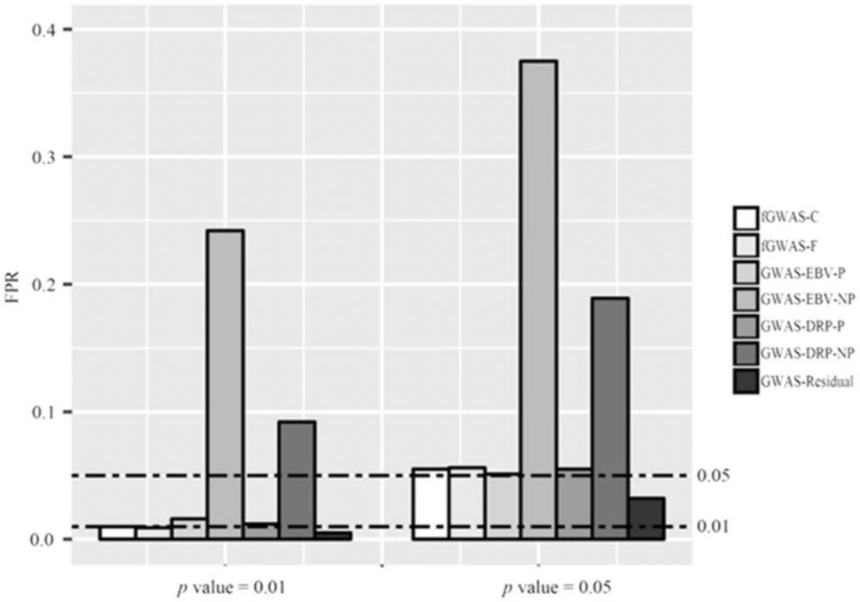
SABRE-TP

- Historically genotyping has focused on bulls and phenotypic data collected from cows.
- The **number of genotyped females** is now rapidly **increasing**

= Own performance records

= Own performance records -> provide direct phenotype measurements

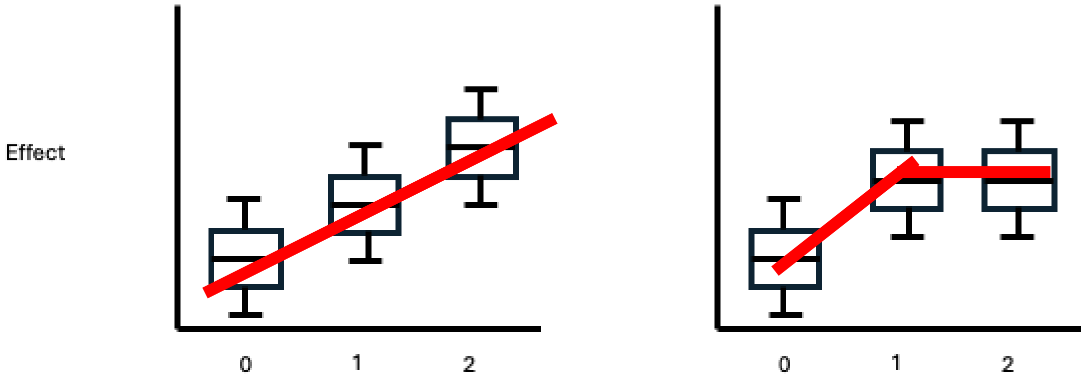
- **More accurate** analysis

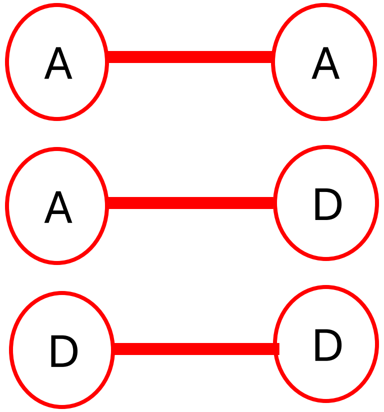


(Ning et al., 2017)

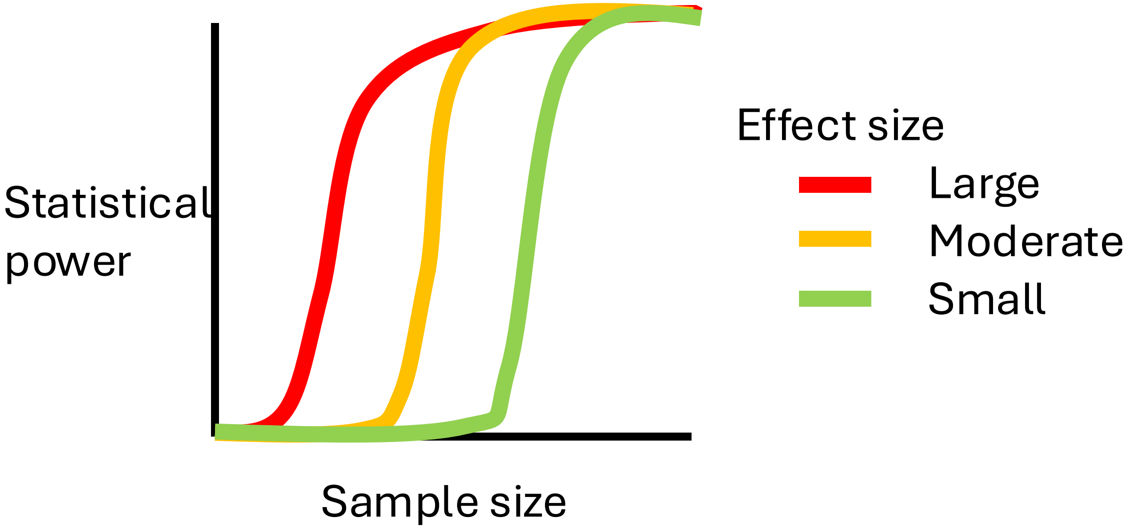
= Own performance records -> provide direct phenotype measurements

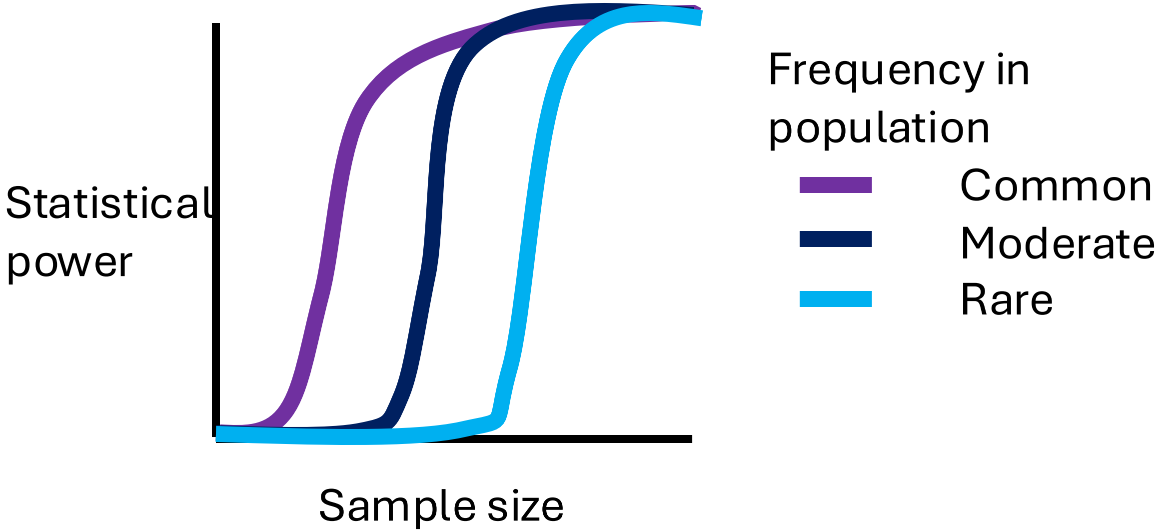
- **More accurate** analysis
- Allow detection of **additive and non-additive** genetic components





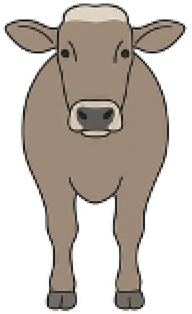
- The **number of genotyped females** is now rapidly **increasing.**
  - Increase in **sample size** = increase in **statistical power**



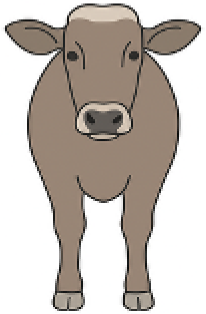


Data

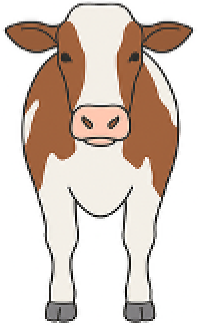
Holstein



Brown Swiss



Orig. Braunvieh

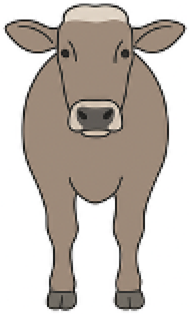


Simmental

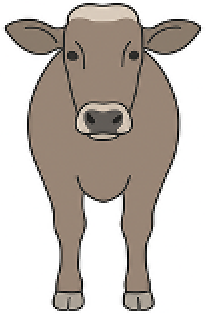
Available genotype data and phenotype records

Data

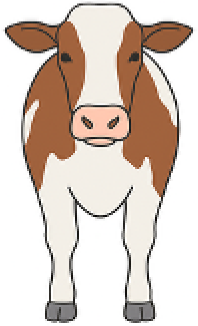
Holstein



Brown Swiss



Orig. Braunvieh



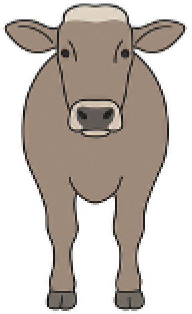
Simmental

Available **genotype data** and phenotype records

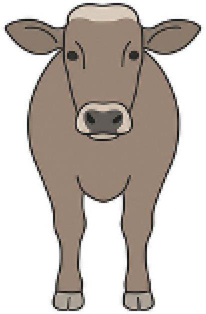
- Genotypes for 179,845 <- ten SNP (20k - 777k SNPs)
- Impute to whole genome sequence level

Data

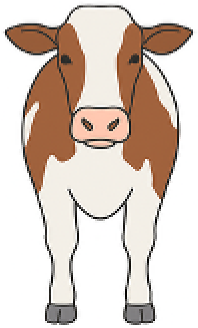
Holstein
N = ~27,500



Brown Swiss
N = ~23,000



Orig. Braunvieh
N = ~4,200

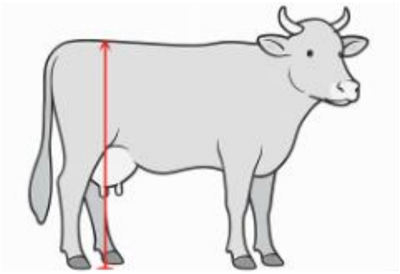


Simmental
N = ~2,900

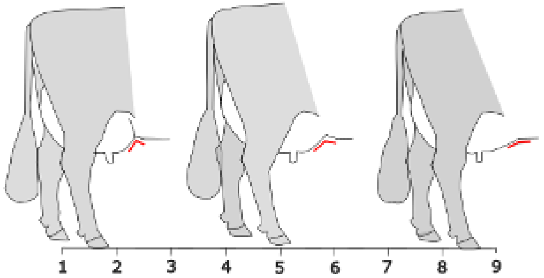
Available genotype data and **phenotype records**

- Linear description routinely performed in the first lactation
- Subset …

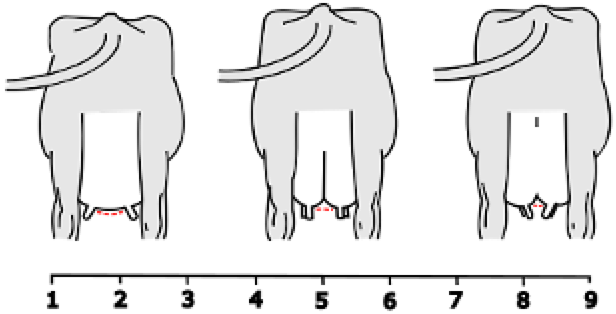
The phenotypes



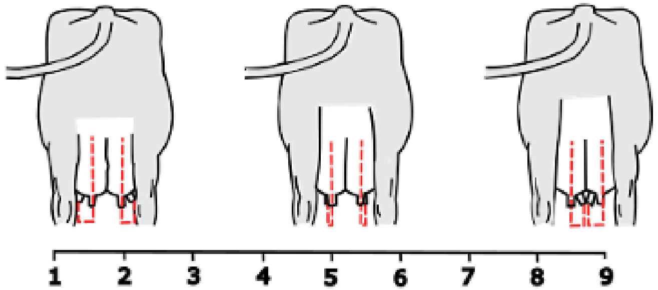
Stature



Fore udder position



Udder central ligament

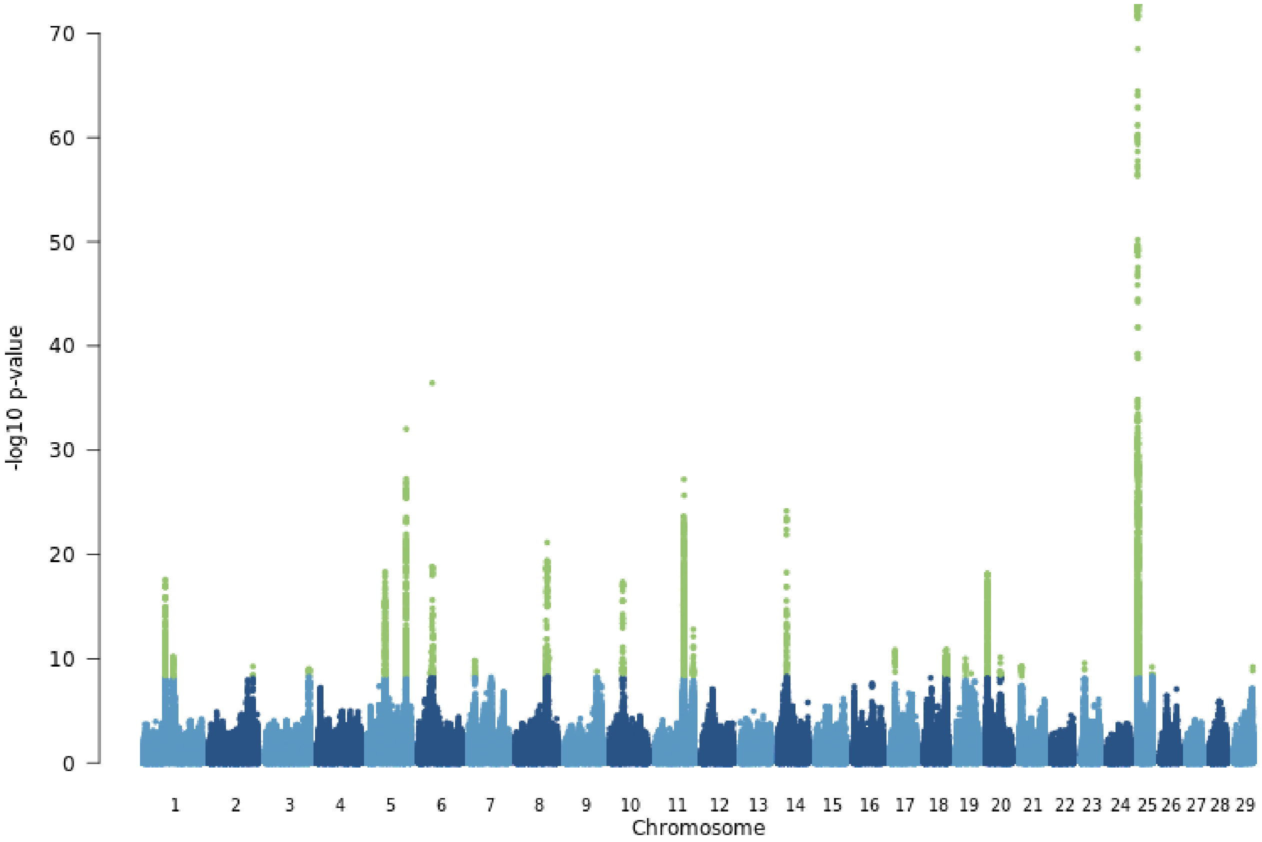


Front teat position

Performed genome-wide association testing within breed -> summary statistics used as input for meta-analysis

- Additive with significant variant-trait associations
- Non-additive did not reveal any QTL that reached the genome-wide significant threshold for mammary morphology.

Stature meta-analysis



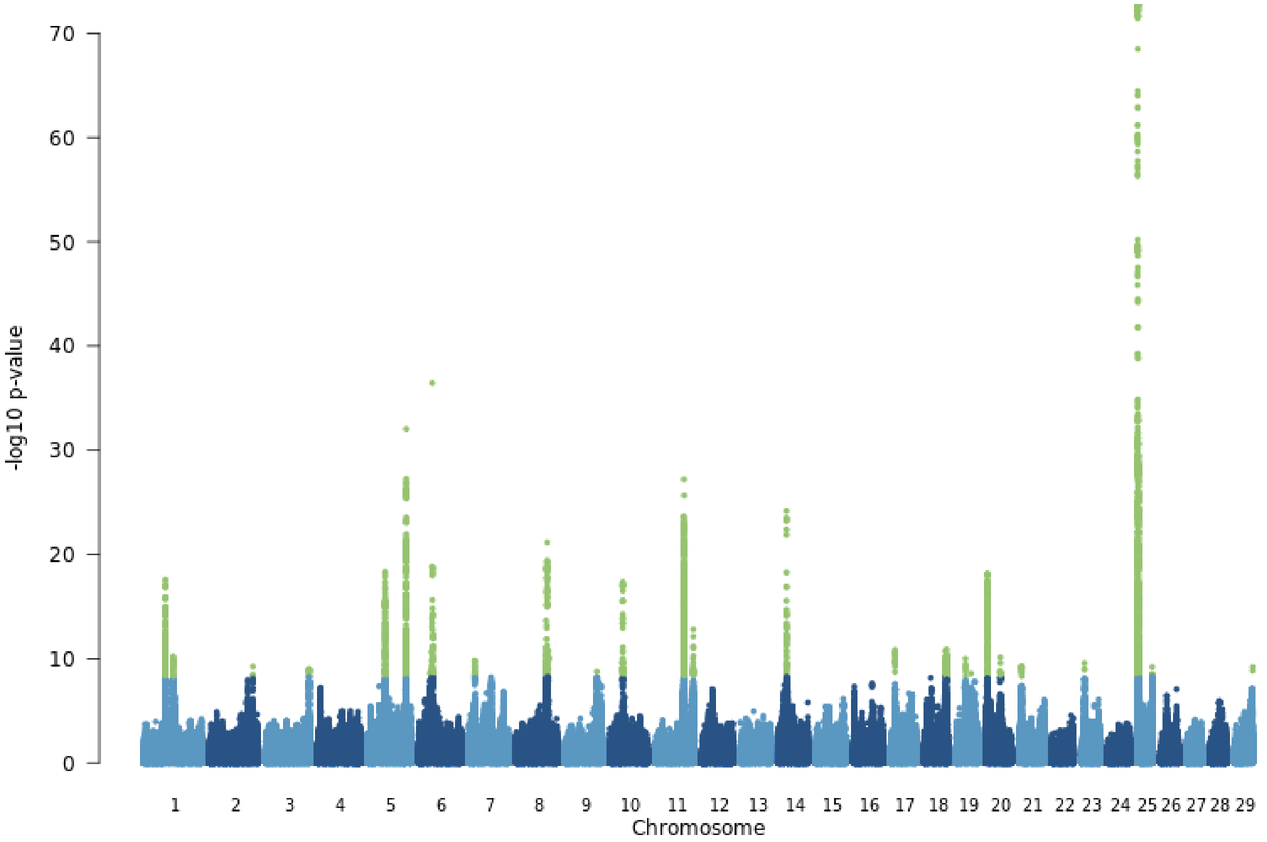
43 stature QTL identified

Comparison with Bouwman et al. 2018

-> 37/43 stature QTL within/around those identified by

-> Regions overlapped with genes associated with stature or body size

Stature meta-analysis

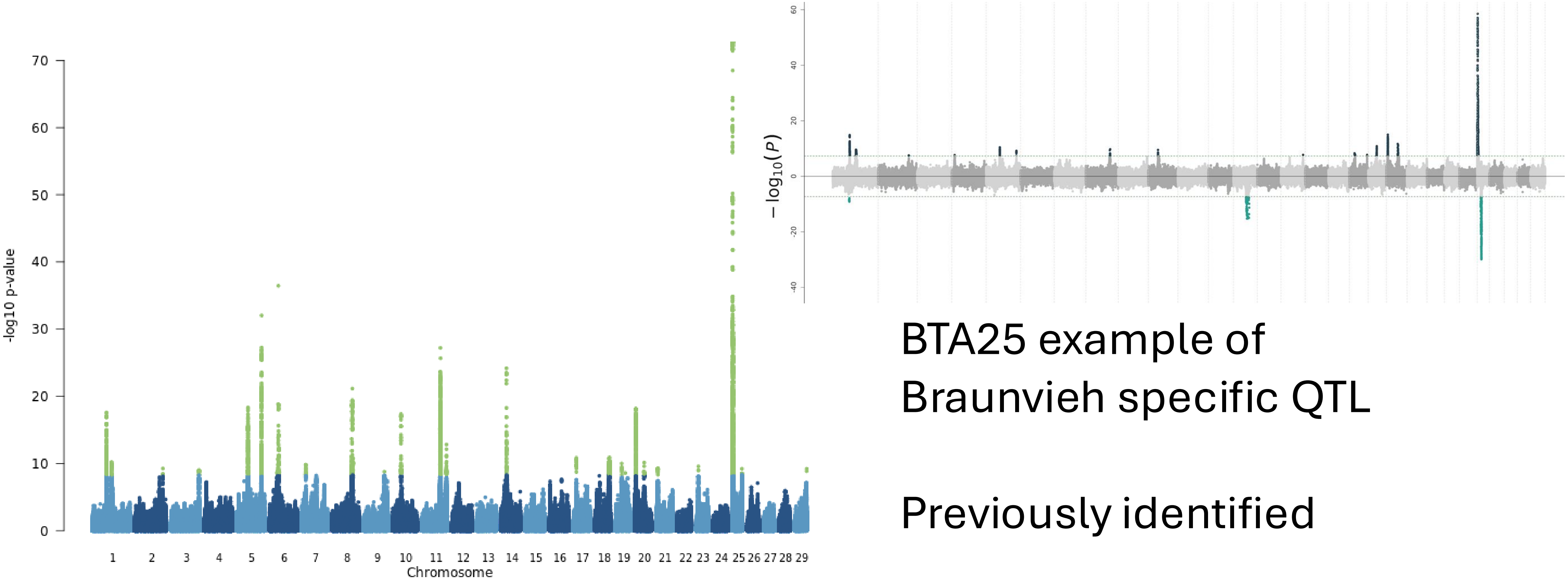


6/43 QTL?

Identified exclusively in Brown Swiss and/or Original Braunvieh

… populations can carry private variants with large effects on complex traits.

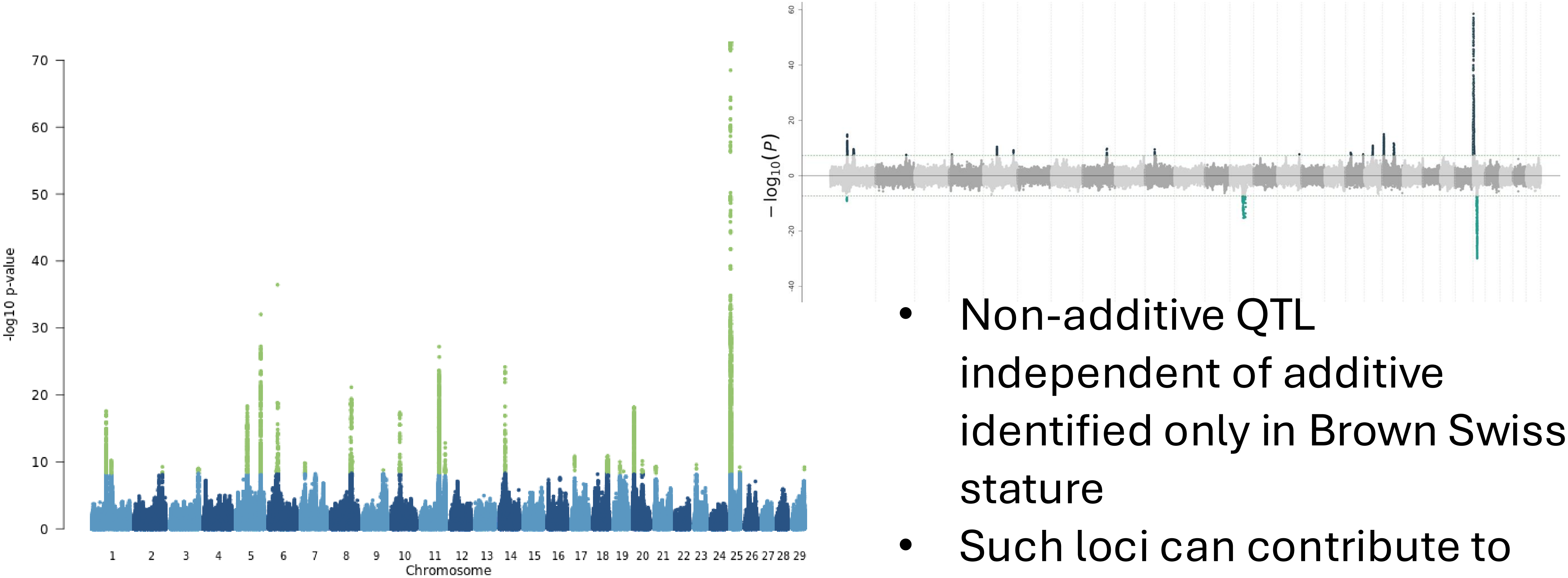
Brown Swiss cattle BTA25



BTA25 example of Braunvieh specific QTL

Previously identified

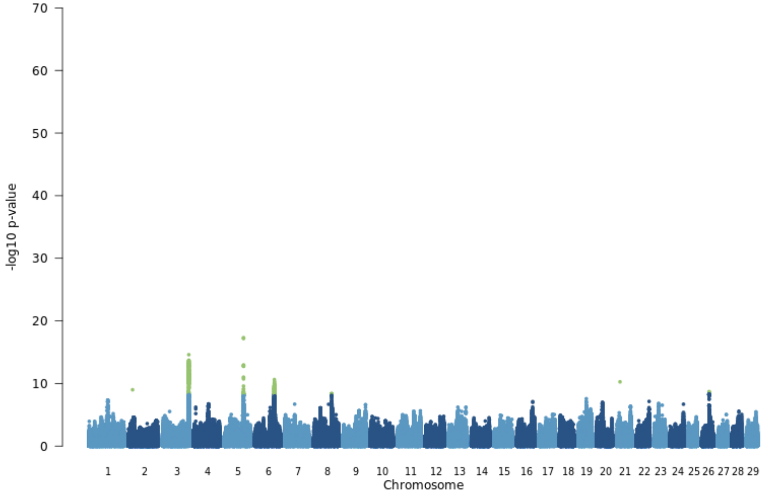
Brown Swiss cattle BTA25



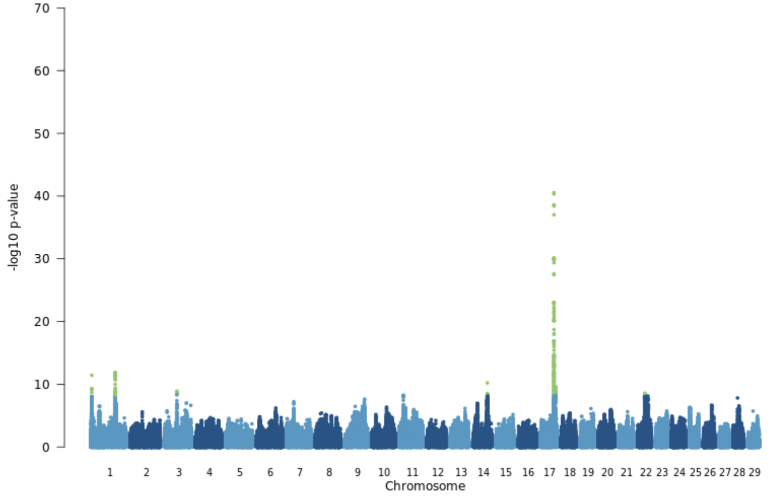
- Non-additive QTL independent of additive identified only in Brown Swiss stature
- Such loci can contribute to inbreeding depression

Meta-analysis - Mammary gland morphology

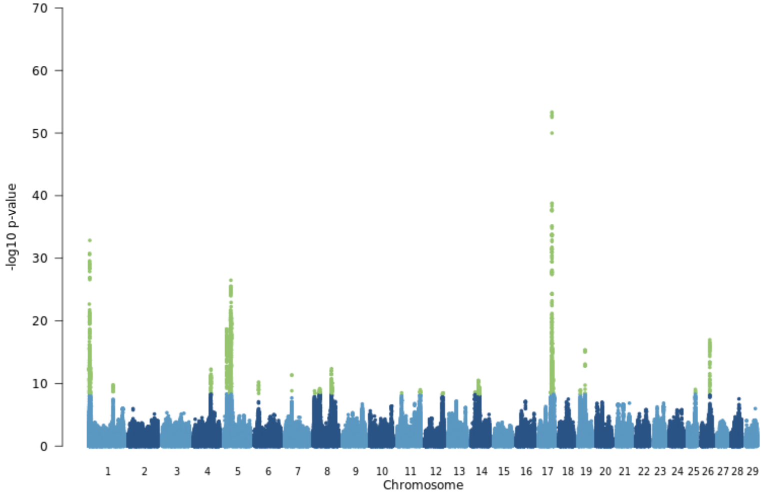
Fore udder



Central ligament



Front teat



- Signals were shared

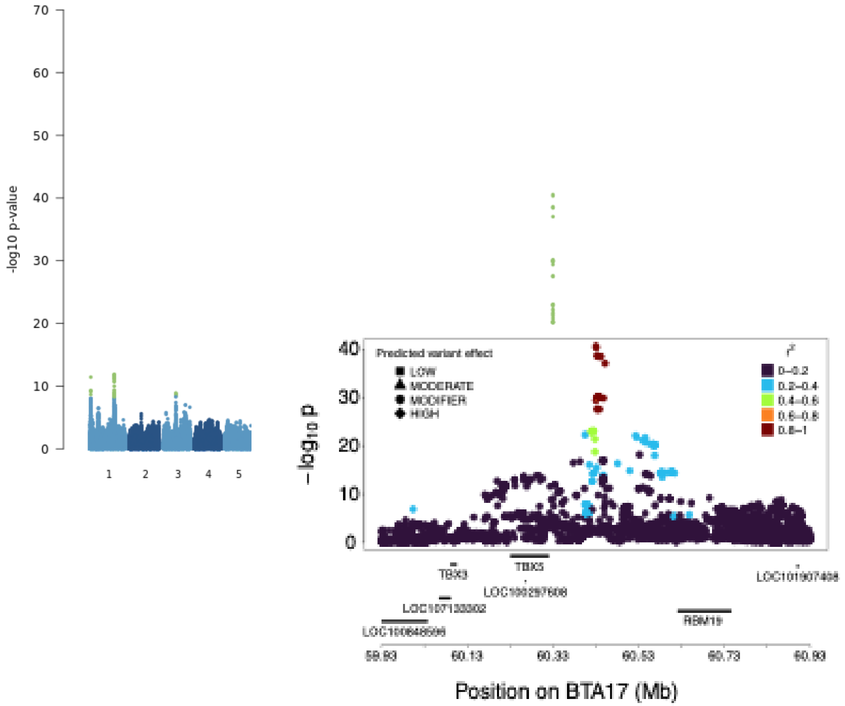
-> pleiotropic effects on mammary gland morphology - well-known influence of the shape of the central ligament on teat positioning.

Mammary gland morphology BTA17

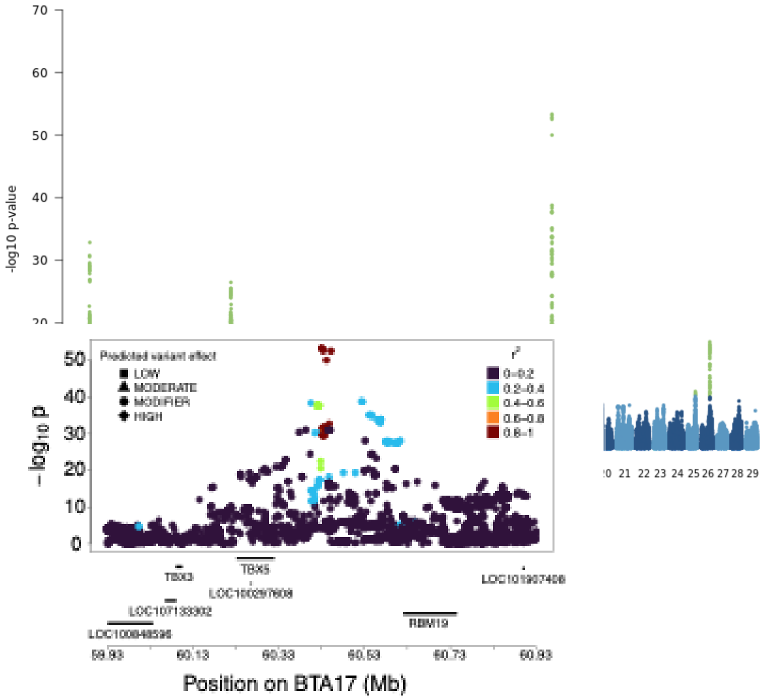
Most significant association on Chr17:60,427,314

- Intergenic region between *TBX5* and *RBM19*
- QTL has previously been implicated

$P_{CL} = 2.84e-41$



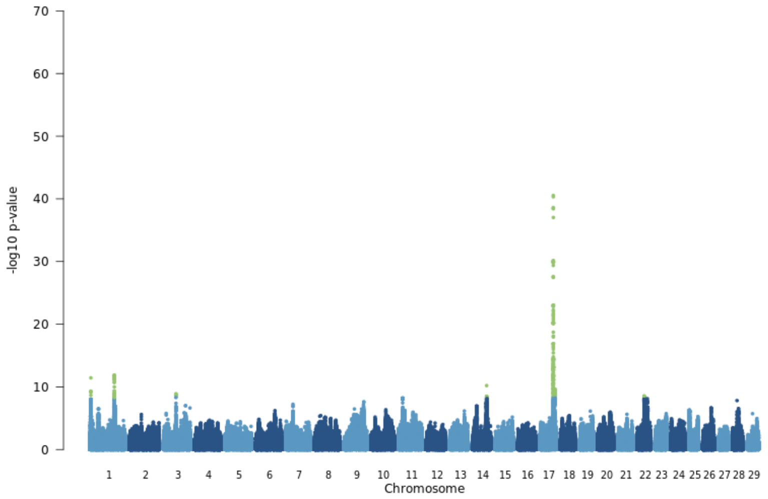
$P_{FT} = 4.53e-54$



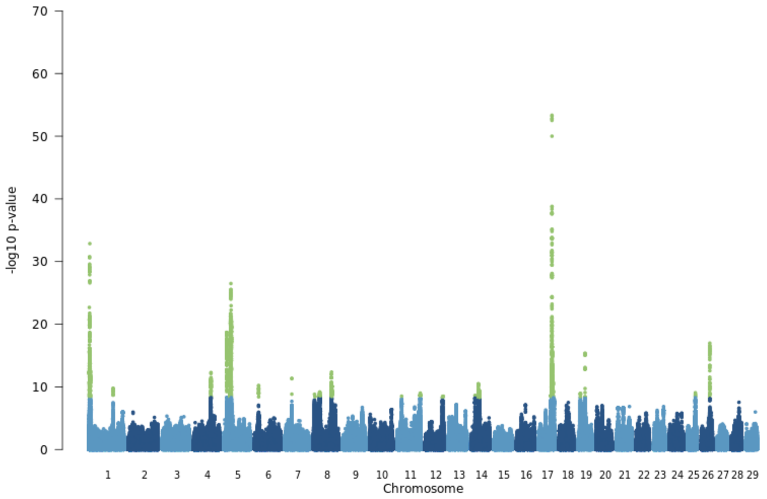
Mammary gland morphology BTA1

Most significant association observed at Chr1:3,063,563

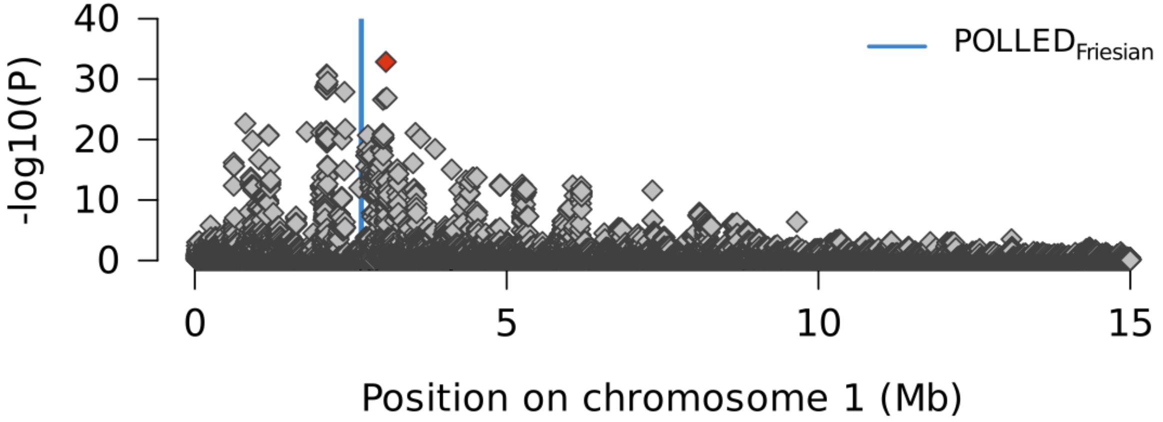
P_{CL} = 3.66e-12



P_{FT} = 1.39e-33



Mammary gland morphology BTA1



The breed-specific GWAS identified only in Holstein cattle

QTL overlaps with Friesian polled variant …

Medugorac et al. 2012 - Bovine Polledness

Found a complex 202 bp insertion-deletion event to polled phenotype in various European cattle breeds = Celtic variant

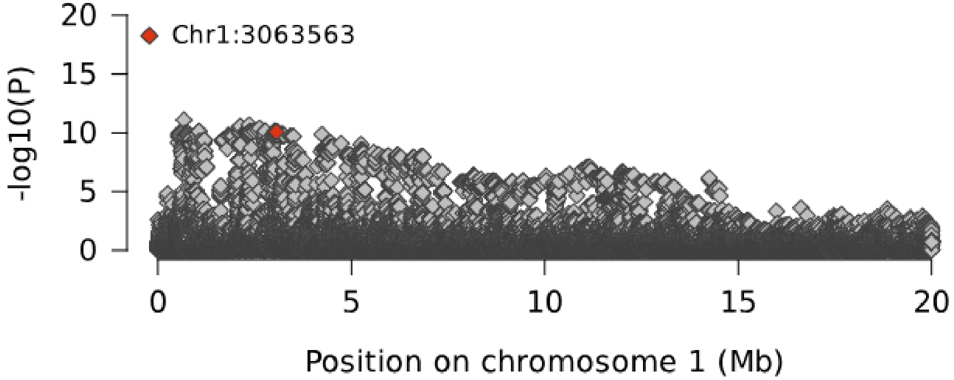
-> expect Holstein Friesian

Further identified Friesian haplotype = 80 kbp duplication on chromosome 1

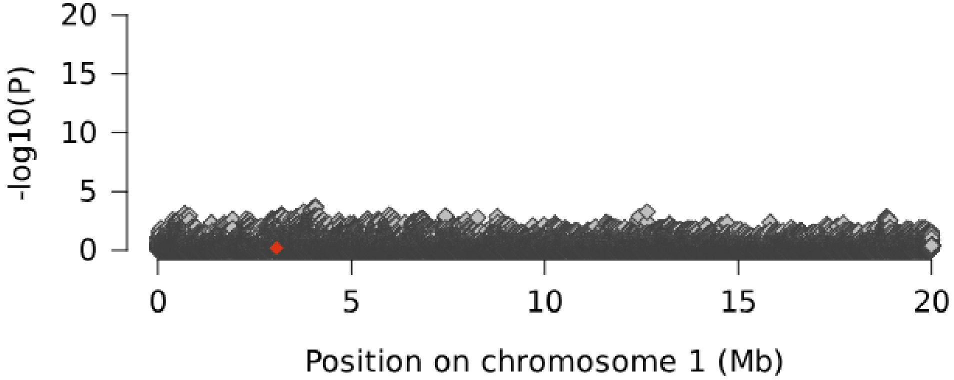
Polled or not polled

- **Variant has been routinely genotyped** in Swiss cattle using the Axiom genotyping array since 2021.
- **3,397**/27,562 3,397 had Axiom-derived genotypes **available**.
  - 304 were heterozygous carriers (POC)
  - 20 were homozygous carriers (POS)
  - allele frequency of 5.06%.
- We **repeated the GWAS for front teat position using animals with known polled genotypes**.

GWAS with known polled genotypes



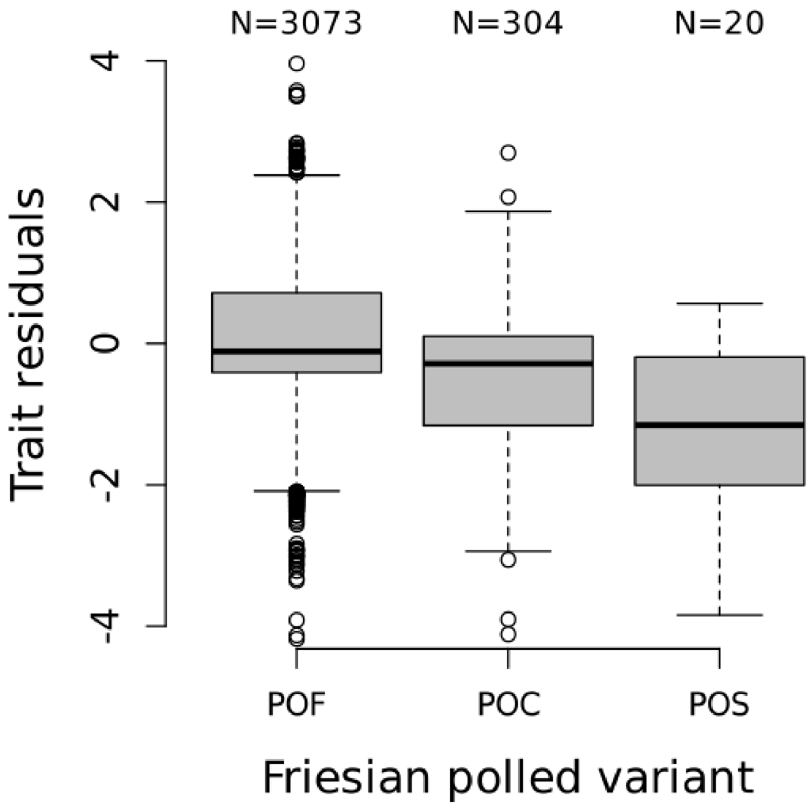
GWAS polled cows the association remained significant



GWAS POF cows (not polled) the association was completely absent.

= Friesian polled variant—or the haplotype containing it—is responsible.

Effect on front teat position



- **Strong association** (p=3.56e-21)
- Each copy reducing the trait score by approximately **0.5 points (additive effect)**
  - POF cows 5.26
  - POC cows 4.71
  - POS cows 3.85

= Carriers of the Friesian polled variant have more **widely spaced front teats and a weaker central ligament**.

Friesian polled allele/haplotype?

- QTL is either due to the Friesian POLLED **variant itself or variant in high linkage disequilibrium.**
- Fine-mapping efforts in **cohorts much larger are required**.

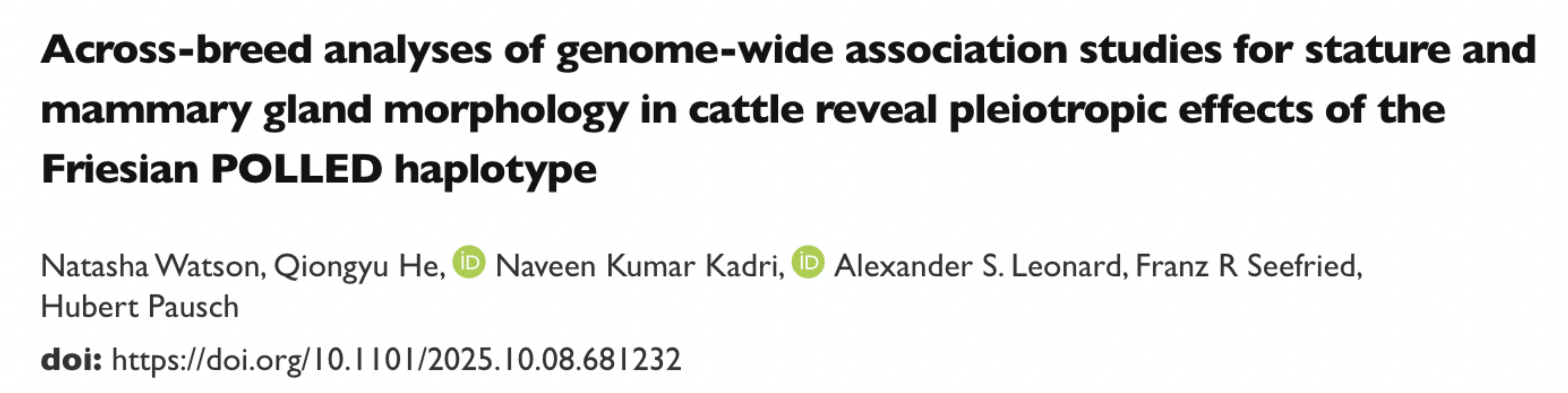
Polledness is also selected for in Brown Swiss?

- But no QTL overlapping the POLLED region was detected in Brown Swiss …
    - However, polledness in **Brown Swiss is conferred by the Celtic variant**
    - Smaller sample size

What does that mean?

- **Monitoring of consequences** associated with POLLED alleles / haplotype with important traits.
- Need for careful monitoring of potential unintended consequences associated with strong selection.
- However, because traits such as mammary gland morphology are highly polygenic, **selection strategies can likely offset** the undesirable effects associated with the Friesian POLLED haplotype.

Thank you!



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Natasha Watson, Qiongyu He, Naveen Kumar Kadri, Alexander S. Leonard, Franz R Seefried, Hubert Pausch

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Bull Fertility
Research Network

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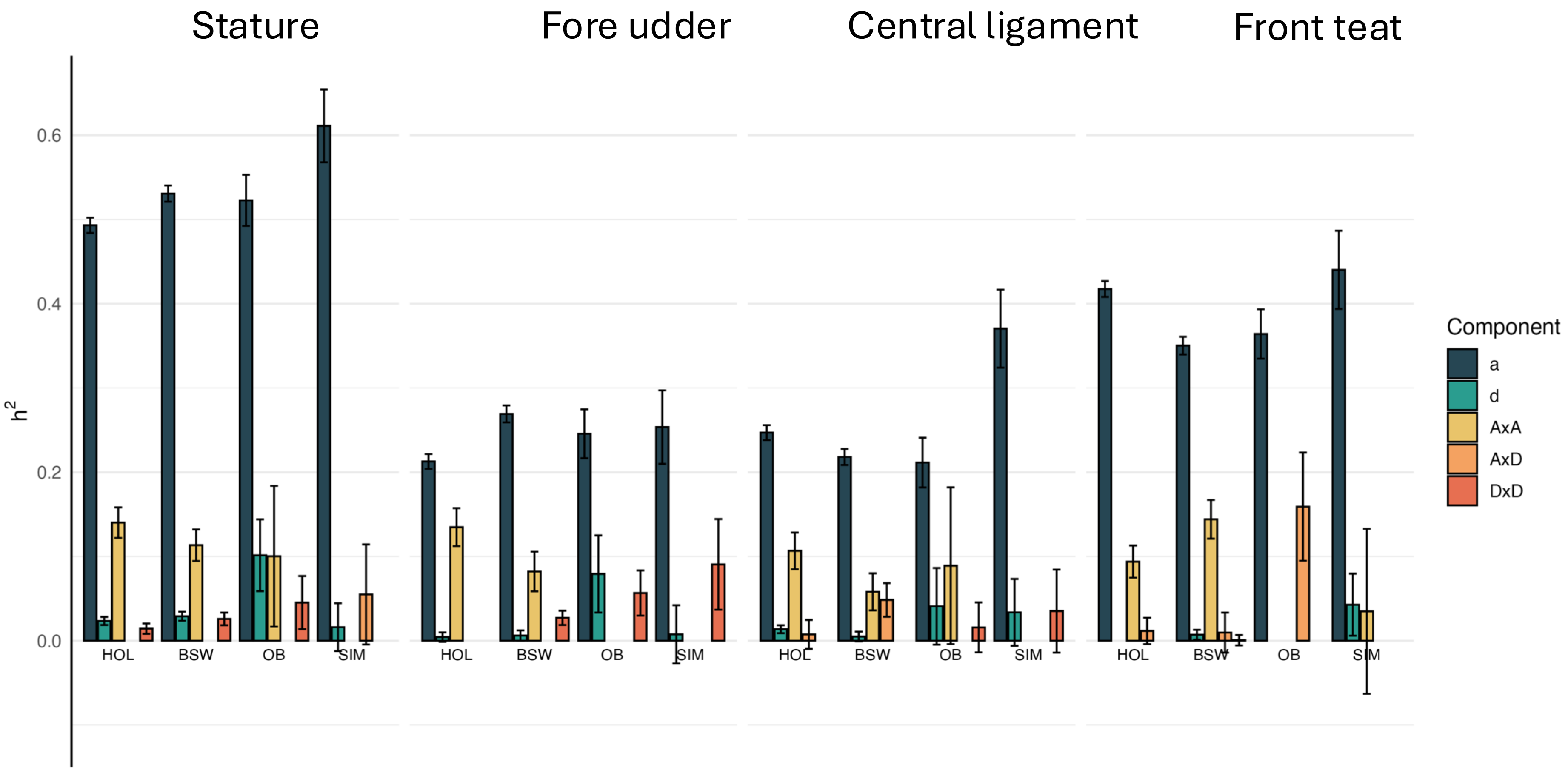
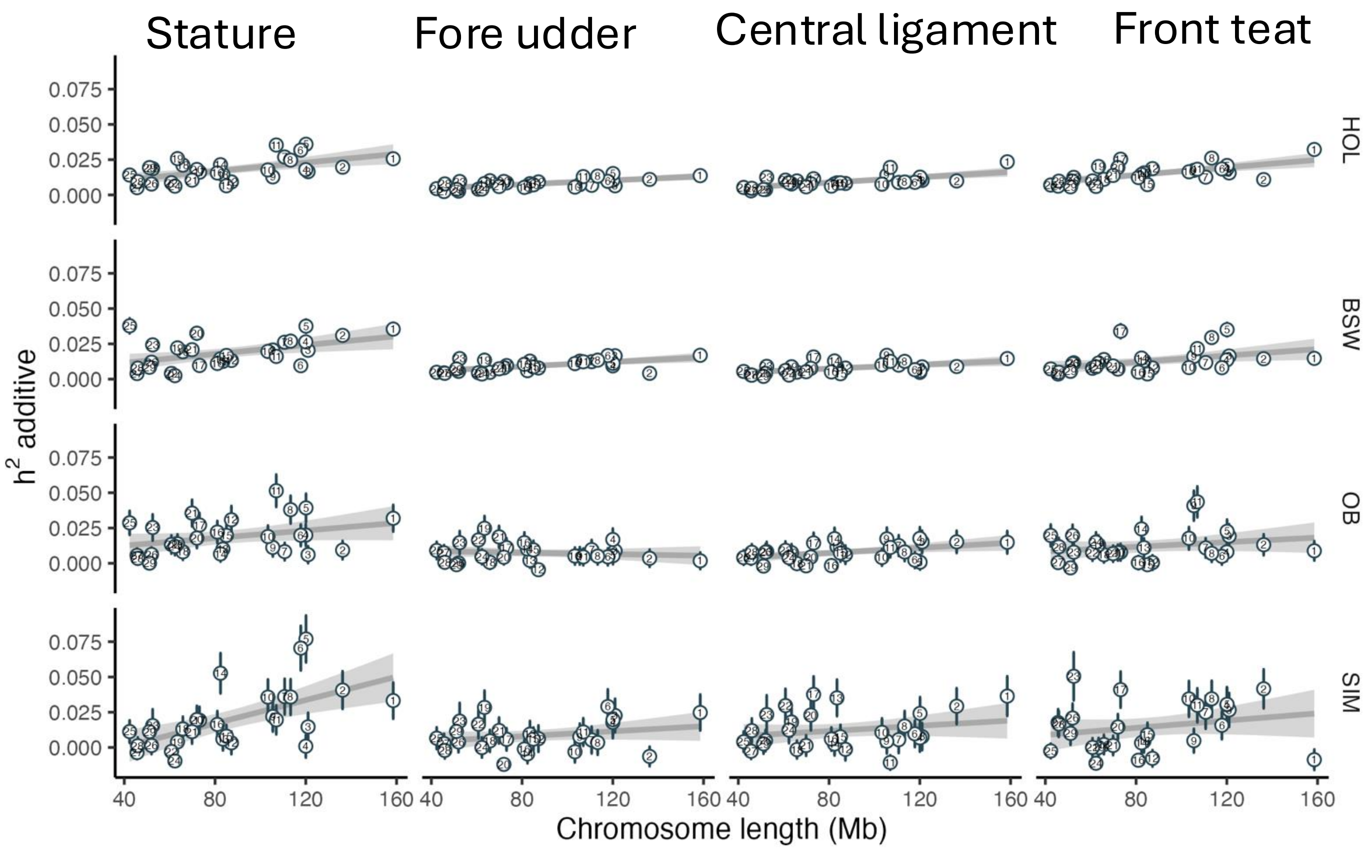
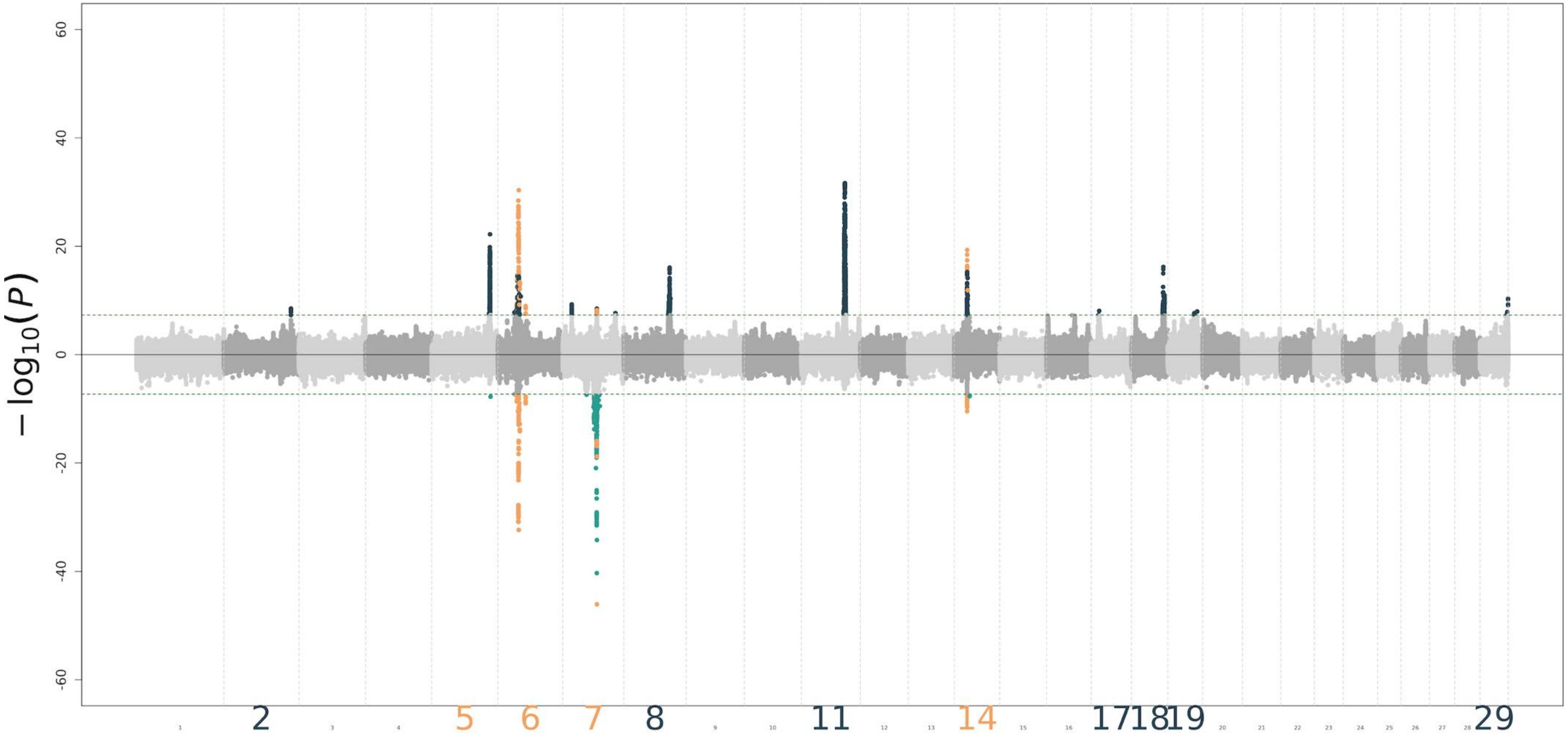
Heritability



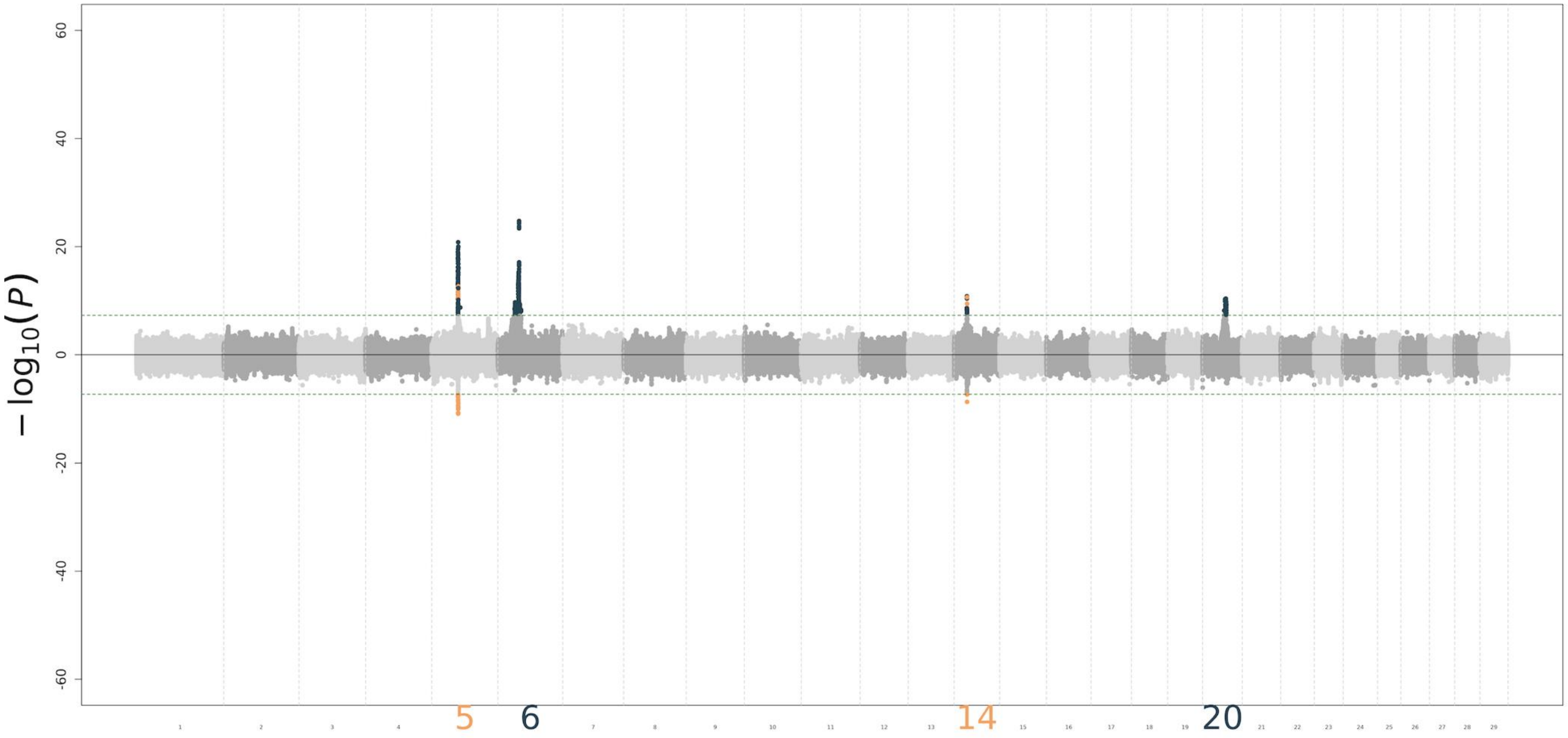
Heritability – Partitioned by chromosome



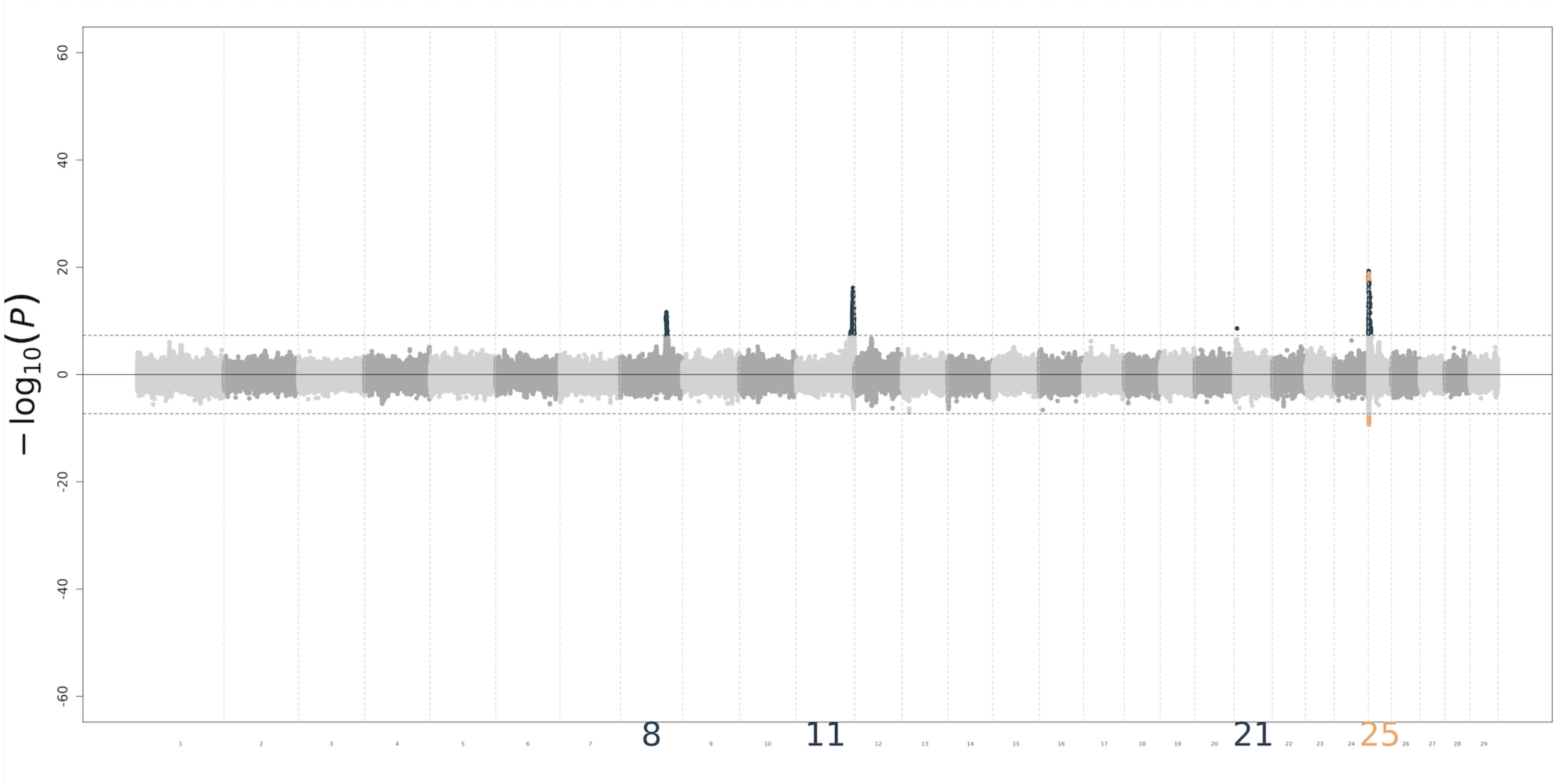
Holstein stature



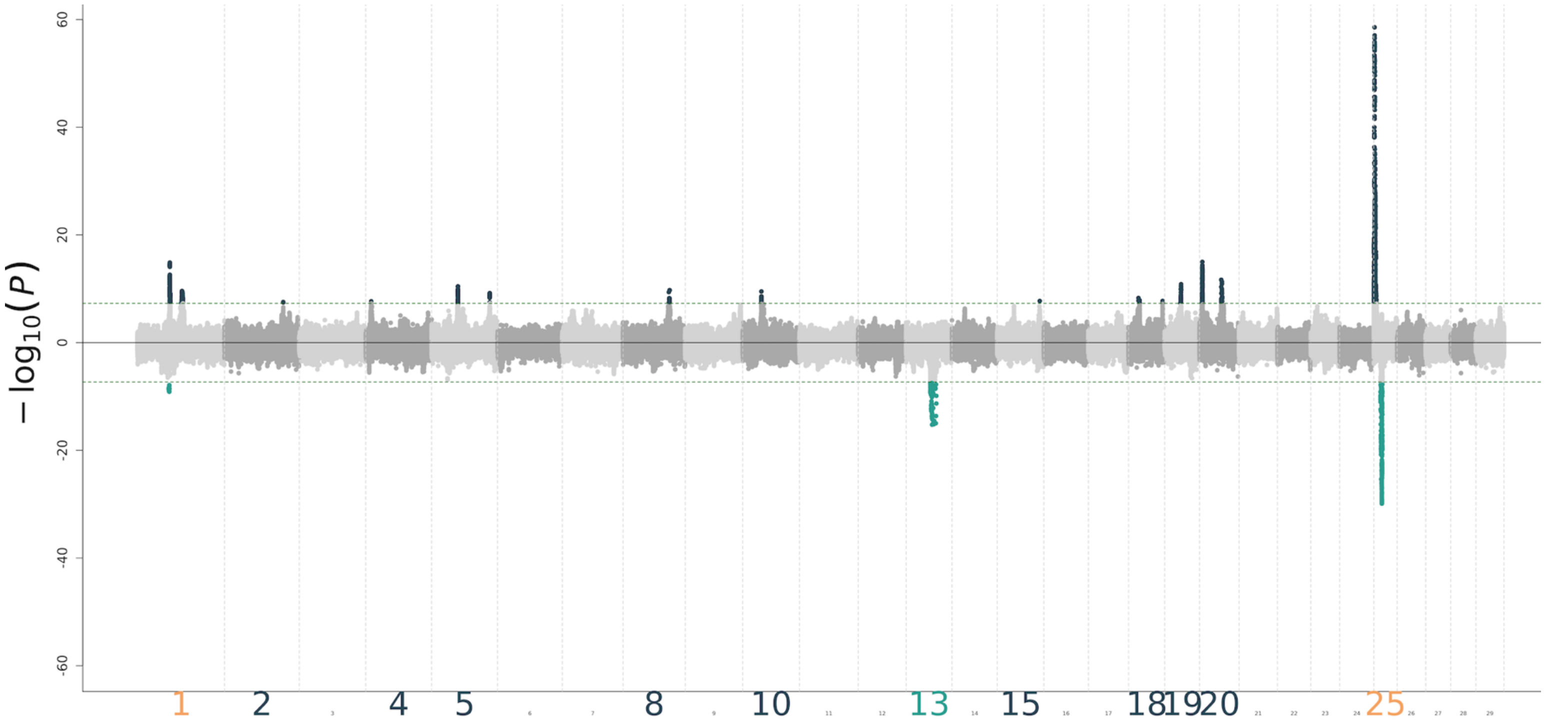
Simmental stature



Original Braunvieh stature



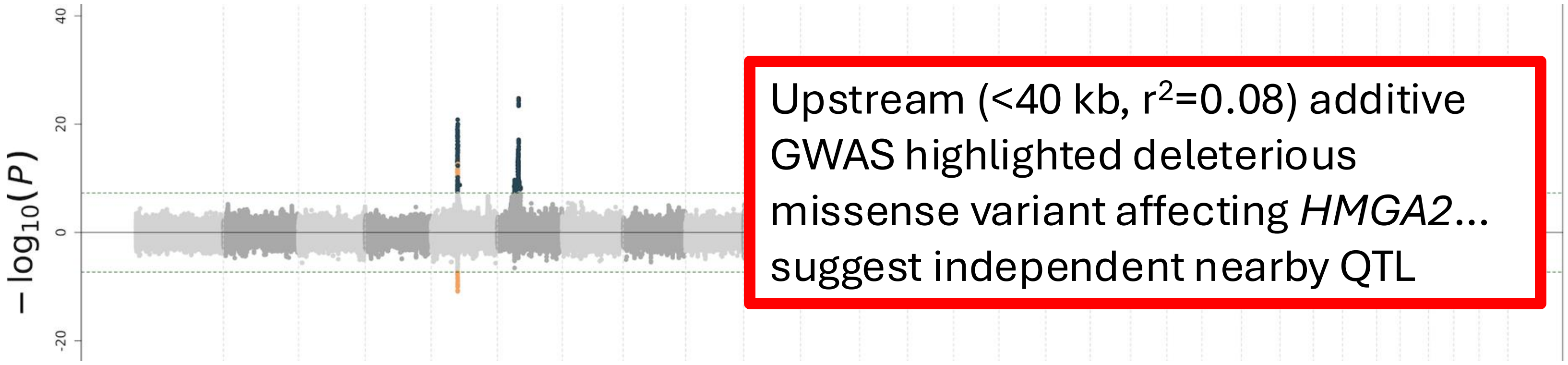
Brown Swiss cattle stature



GWAS – stature dominance

- Revealed QTL that were not detected with the additive model.
  - Variants / QTL segregated by breed:
    - Holstein BTA7 - missense variant in *ARS1* (reported as a candidate causal)
    - Brown Swiss BTA1, BTA13, BTA25 (identified in an earlier study)

    - Simmental BTA5

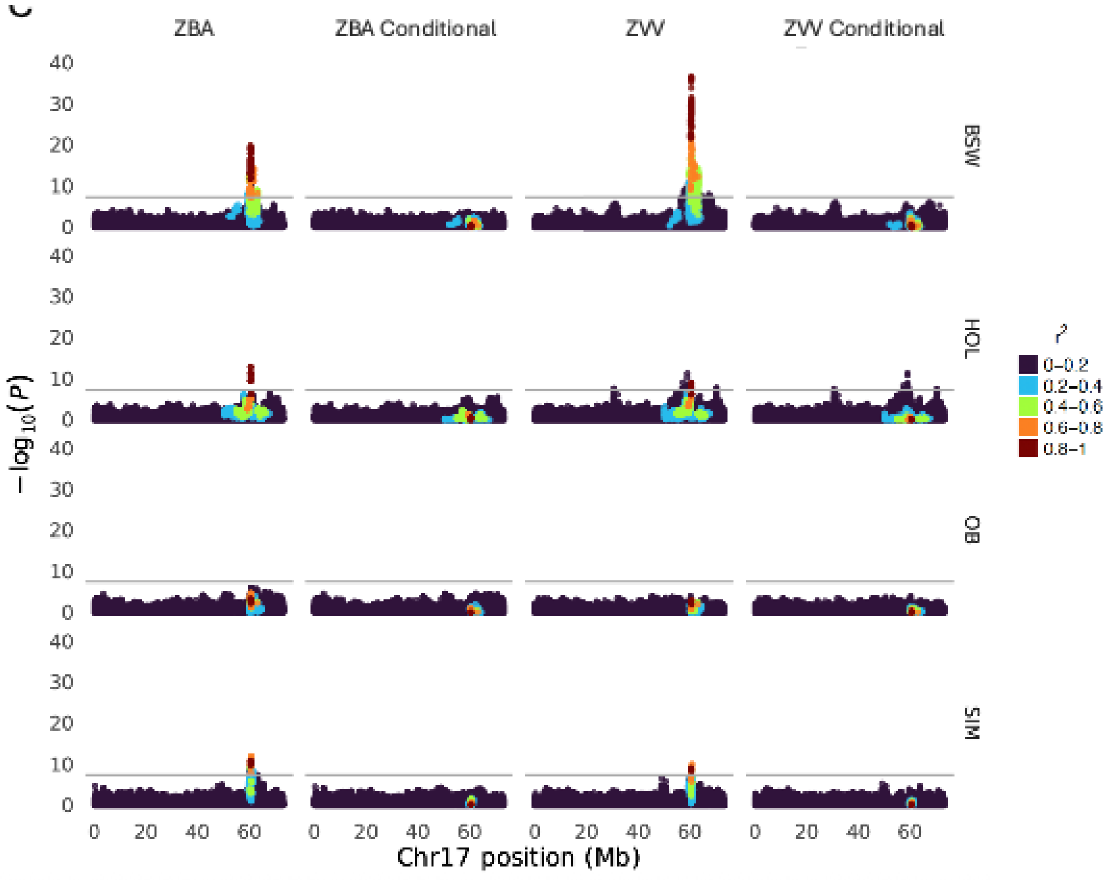


Upstream (<40 kb, r^2=0.08) additive GWAS highlighted deleterious missense variant affecting *HMGA2*… suggest independent nearby QTL

Mammary gland morphology BTA17

Slight differences within breed …

… but all 60.4 MB QTL absent when conditioned on top marker from meta-analysis



Significant variants at 58.9 Mb – possible indicate presence of additional trait-associated variants in region

Smaller population size and smaller allele frequency

High LD in region – conditional remove association within breed