Using expression data to detect small QTL in dairy cattle

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Introduction

- Sequence data → detect causative mutations, use for genomic prediction
- Most QTL have a small effect → difficult to detect
- Many variants associated with gene expression → eQTL → use to detect QTL?

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Objective

Detect variants associated with QTL and eQTL

-Correlate local GEBVs & gene expression

-Colocalisation of QTL and eQTL

Methods: Correlate local GEBVs & gene expression

- Calculate local GEBVs:
    - HD genotypes of 35,775 Holstein, Jersey and crossbred bulls and cows
    - DTD / TD for milk, fat and protein yield, milk and fat percentage, and fertility
    - SNP effects estimated using Bayes R hybrid
    - Sum up SNP effects over 250kb windows
    - Select intervals that explain at least 1/10,000th of the total additive genetic variance

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  - 105 Holstein cows (milk + blood samples) and 26 Jersey cows (milk samples)
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→ Correlate gene expression & local GEBVs, select correlations with $p \leq 10^{-5}$

Methods: GWAS & eQTL

- GWAS
  - Same individuals as used for local GEBVs, imputed up to full sequence data, ~4.8M variants after filtering & LD pruning
  - Mixed linear model association analysis in GCTA (Yang *et al.*, 2011), separate for bulls & cows
  - Meta-analysis of bulls & cow GWAS using weighted z-scores model in Metal (Willer *et al.*, 2010)

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- eQTL analysis
  - Same cows as gene expression
  - ~10 million sequence variants, 12,772 genes in milk and 11,577 in blood
  - For all genes, association of expression level with all variants on the same chromosome

Methods: Colocalisation of eQTL and QTL

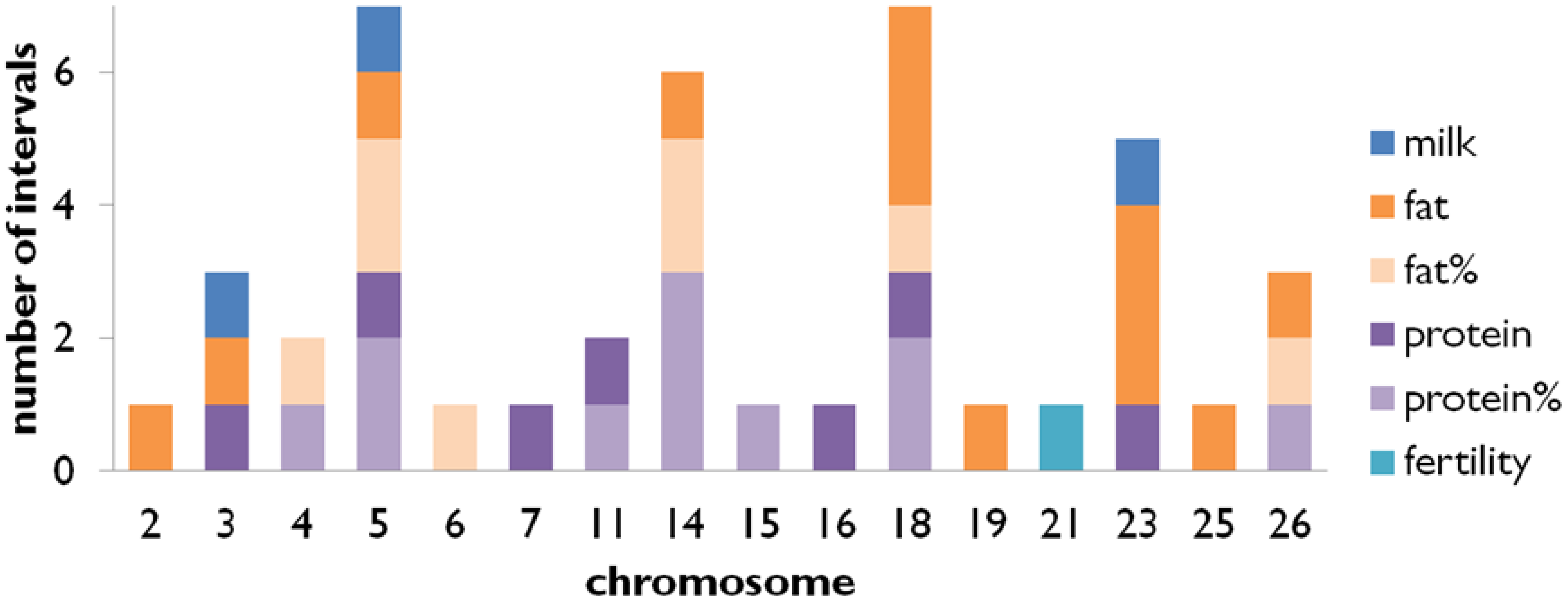
- Colocalisation posterior probability (CLPP) = the probability that the same variant is causal for QTL and eQTL

- eCaviar software (Hormozdiairi *et al.*, 2016)

- CLPP computed based on GWAS & eQTL effects and LD between variants

- CLPP ≥ 0.01 → colocalisation

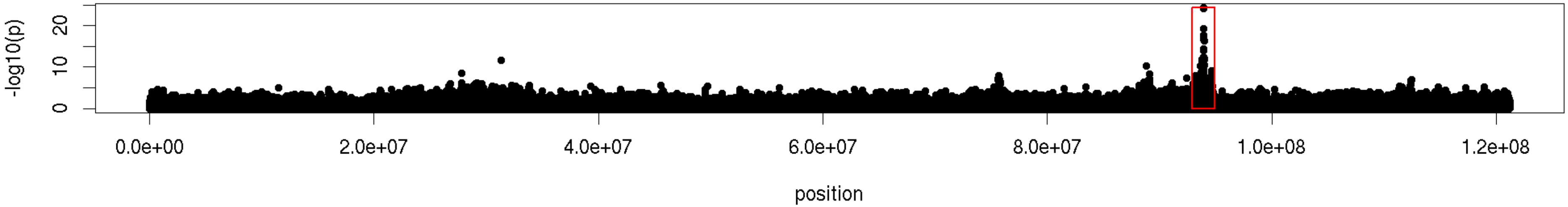
Intervals with significant correlations between local GEBVs & gene expression



Example: MGST1, chr 5, milk yield

Known QTL and eQTL (Littlejohn *et al.*, 2016)

GWAS



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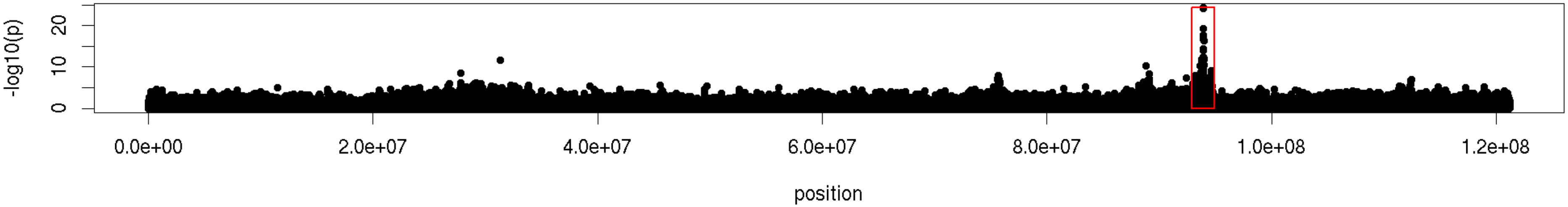
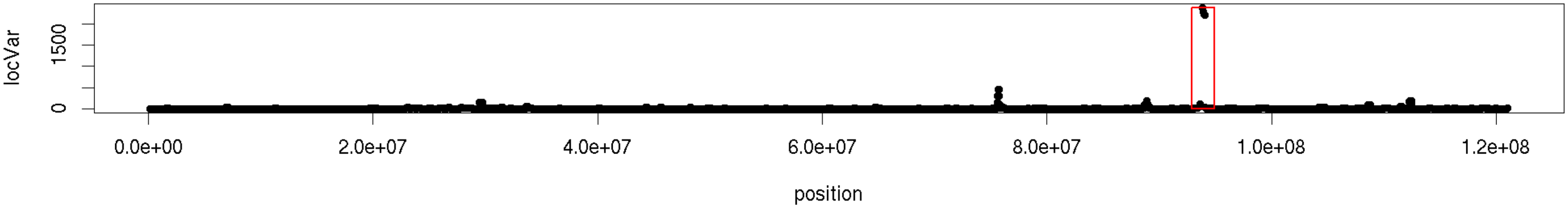


var(locGEBV)



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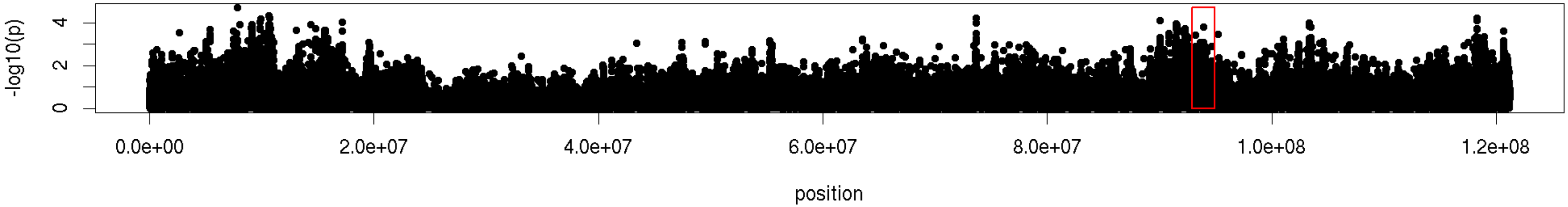
In our study, p=0.008 for eQTL reported by Littlejohn *et al.* → lack of power?

eQTL



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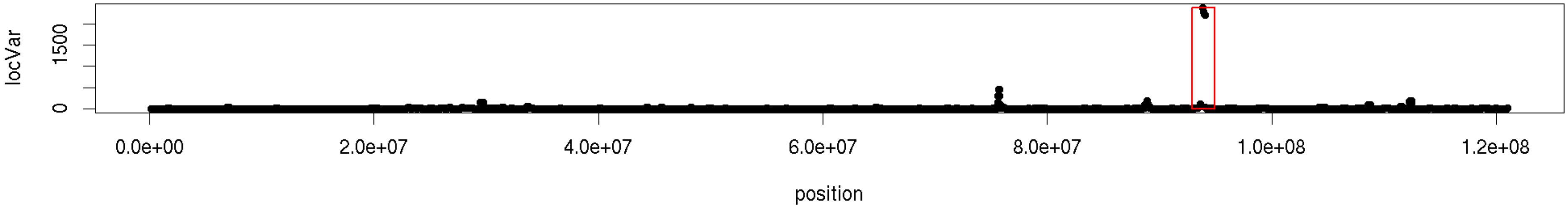

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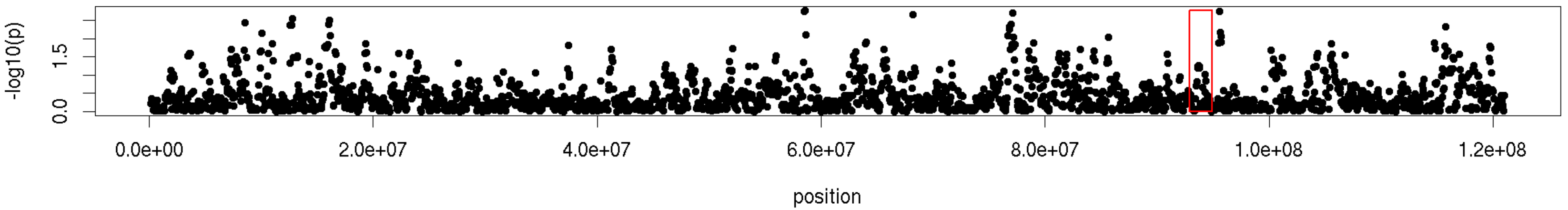
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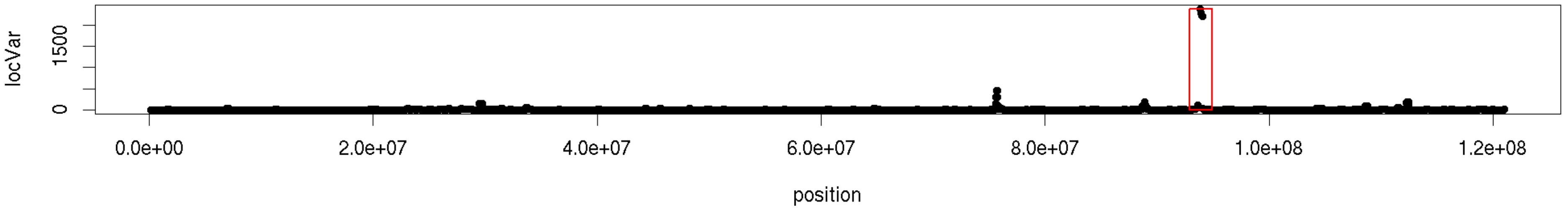
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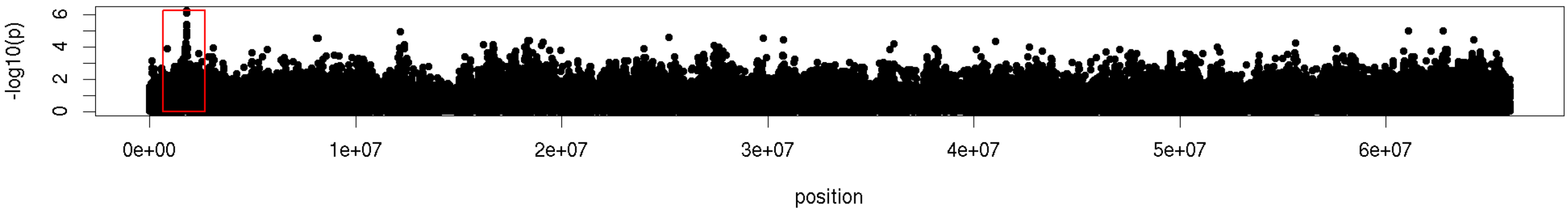
Example: FUK, chr 18, fat yield

Small peaks in GWAS & local GEBV variance

GWAS



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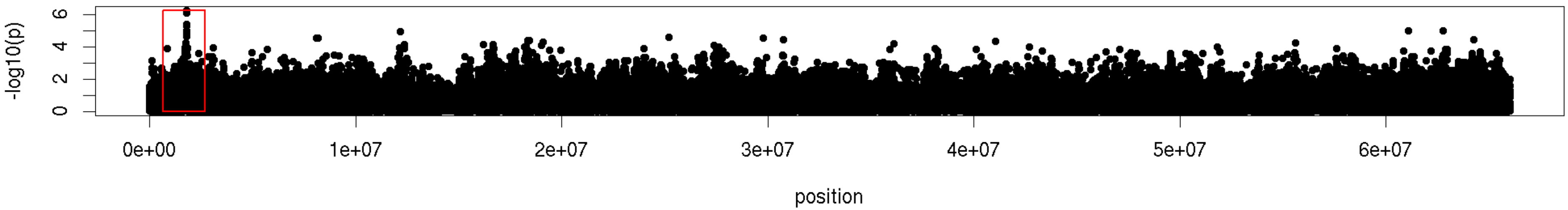

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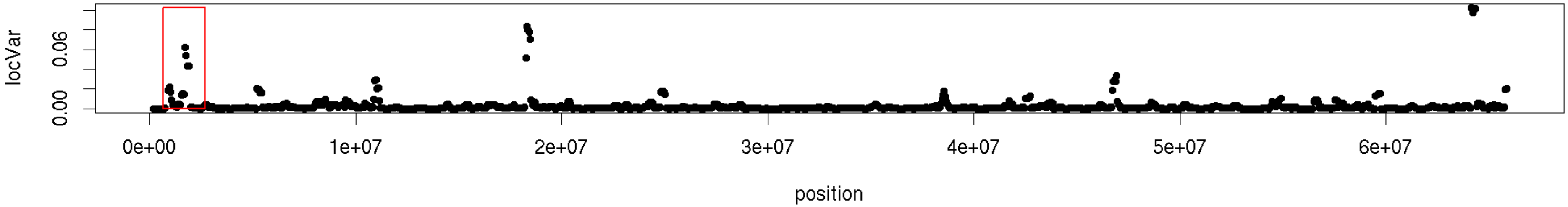

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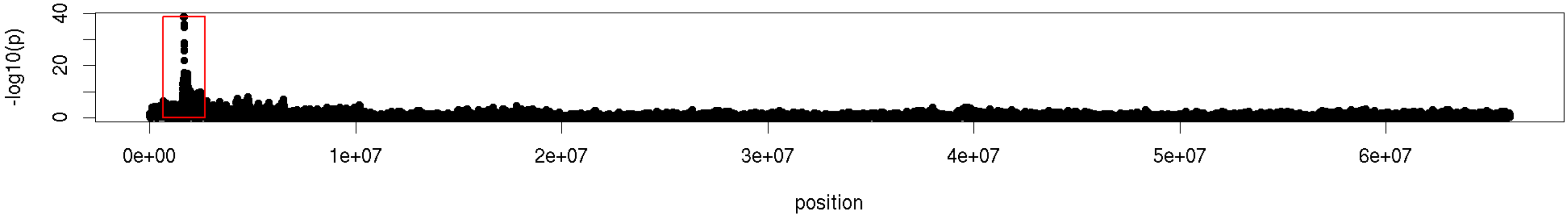
Highly significant eQTL

eQTL



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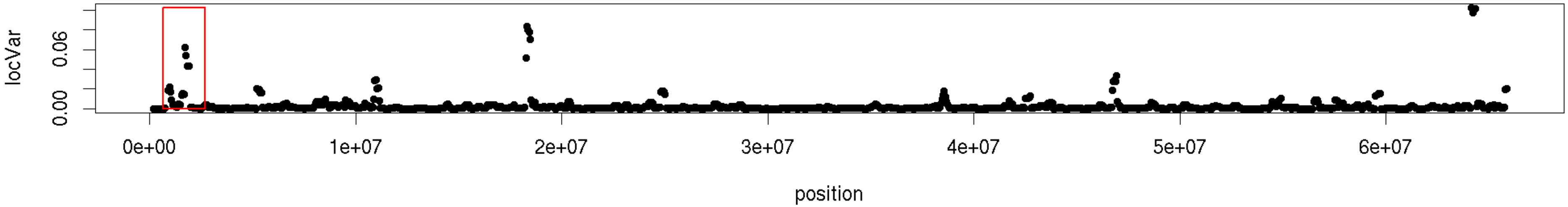

Example: FUK, chr 18, fat yield

Correlation between FUK expression & local GEBVs = 0.90 (p = 5×10^{-39})

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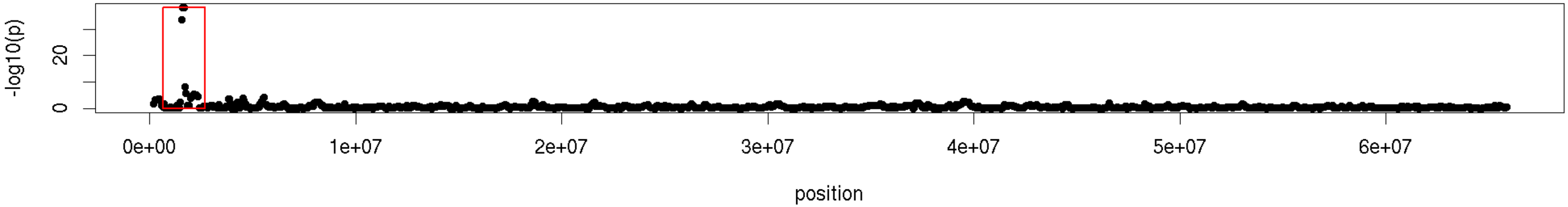

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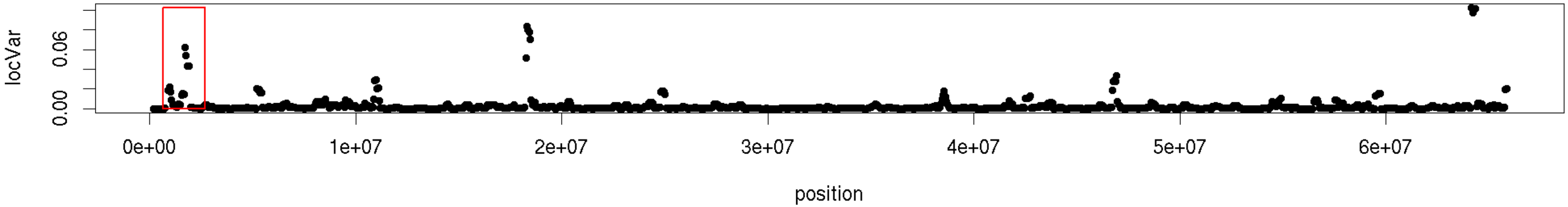

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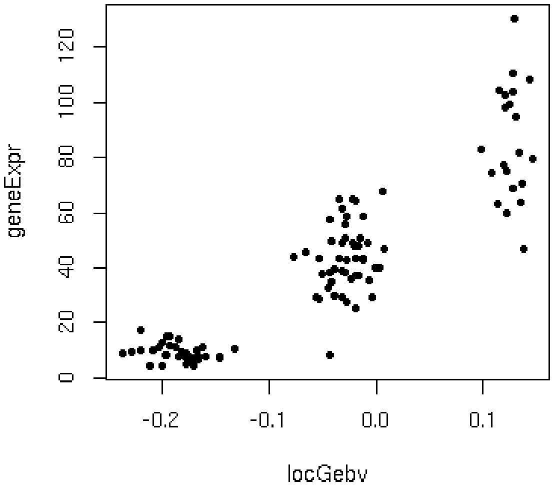
locGEBV vs expression



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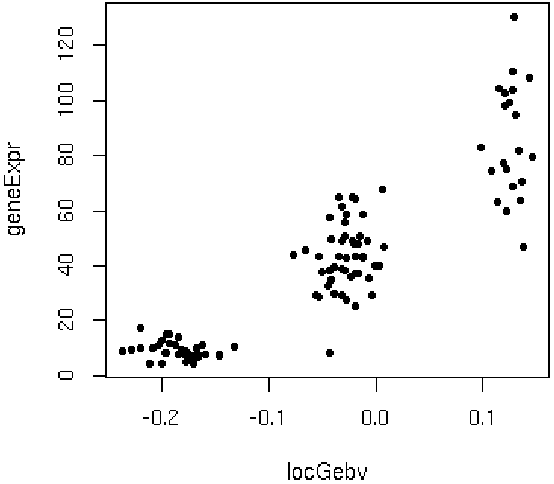
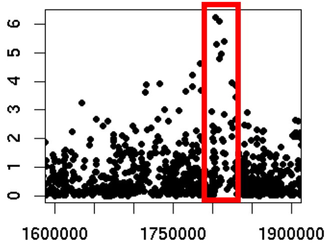


GWAS



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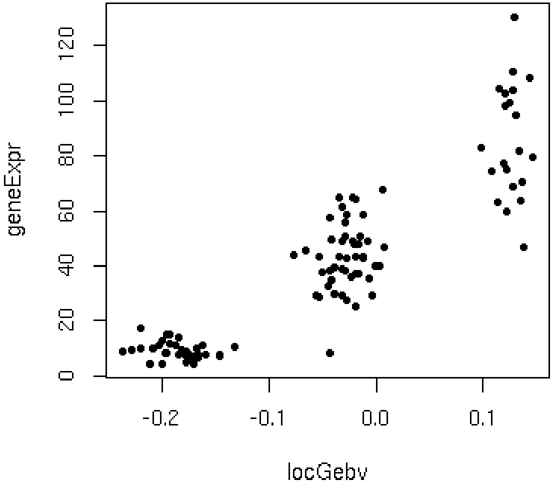

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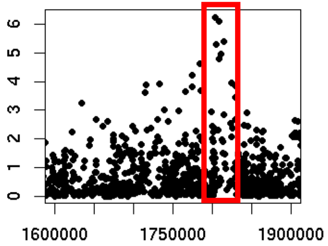
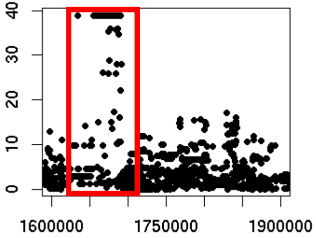


eQTL



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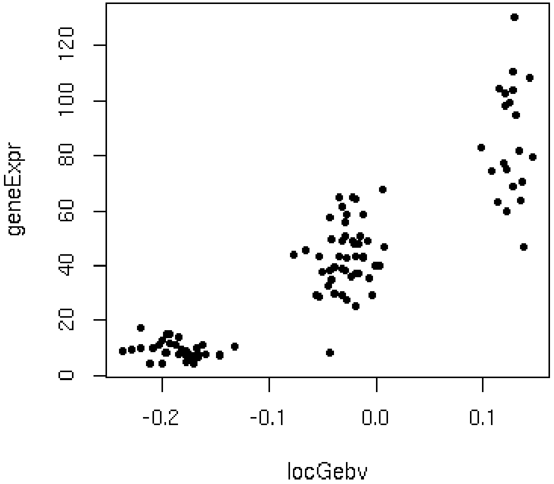

GWAS

eQTL

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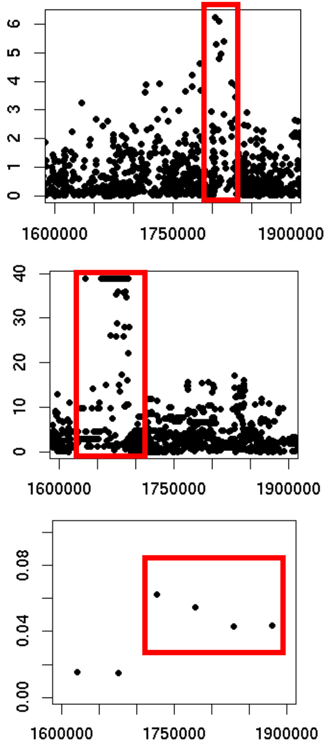

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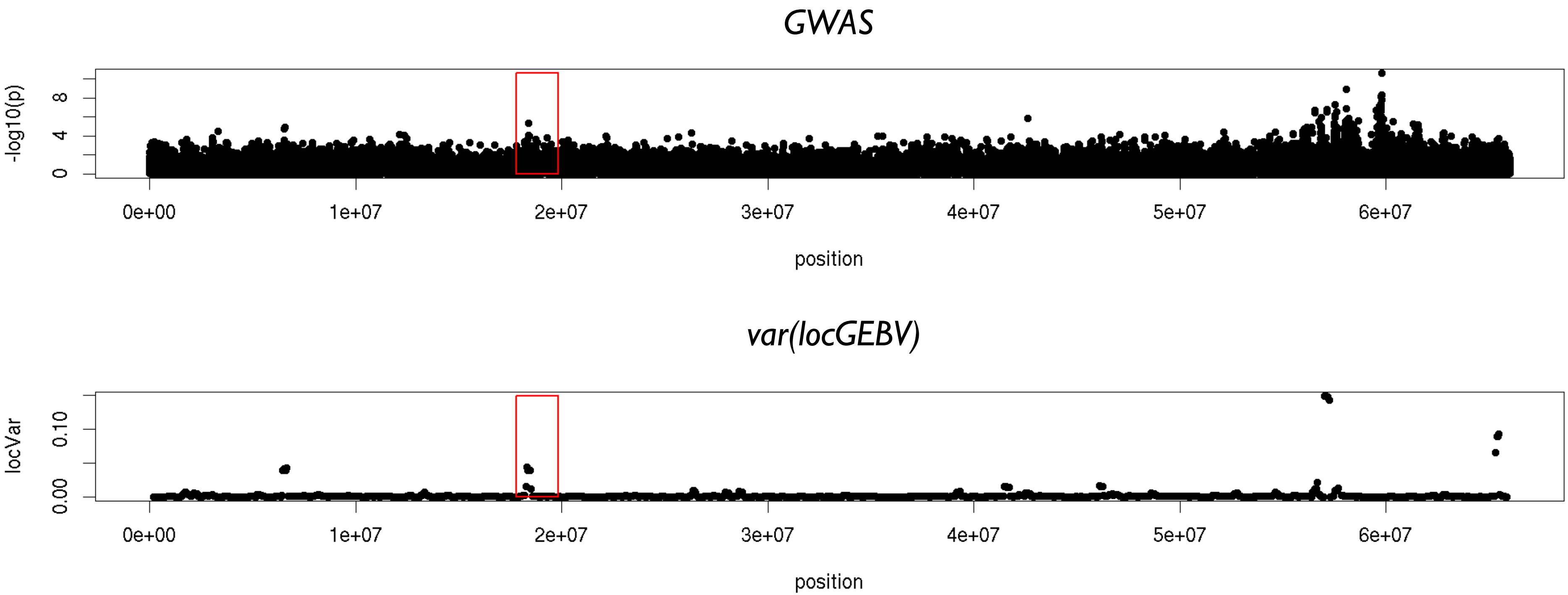
→ The majority of QTL and eQTL do not seem to colocalise, and the ones that do explain only a minor part of the genetic variance

Example: BRD7, chr 18, protein yield

Small peaks in GWAS & local GEBV variance



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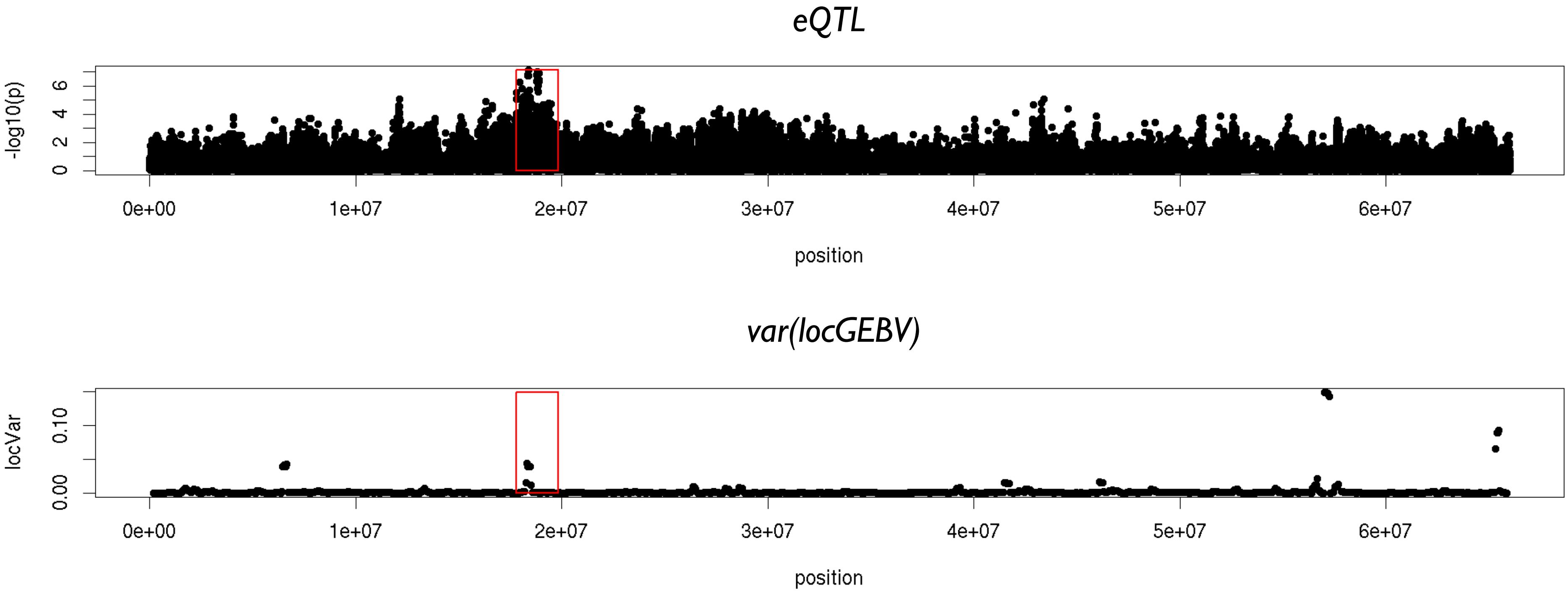
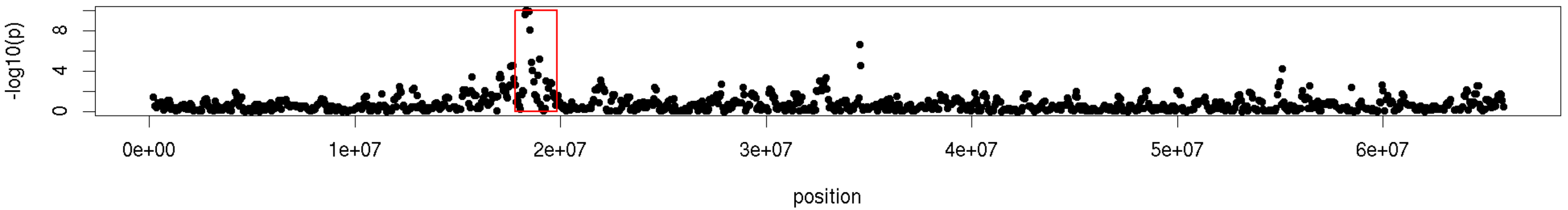
Significant eQTL



Example: BRD7, chr 18, protein yield

Correlation between BRD7 expression & local GEBVs = 0.58 (p = 9.3×10^{-11})



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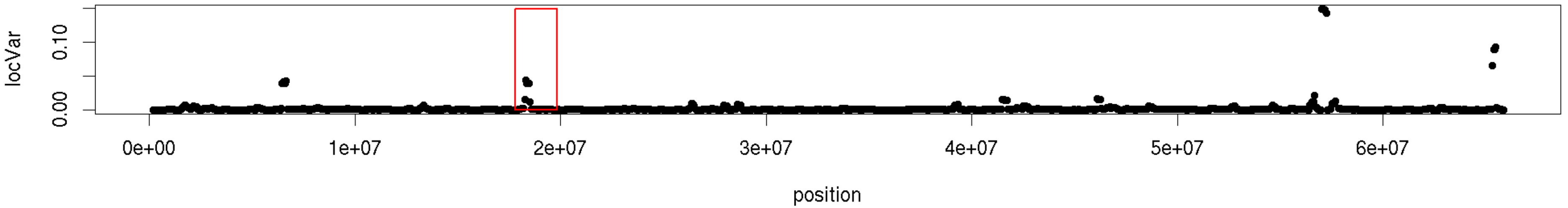

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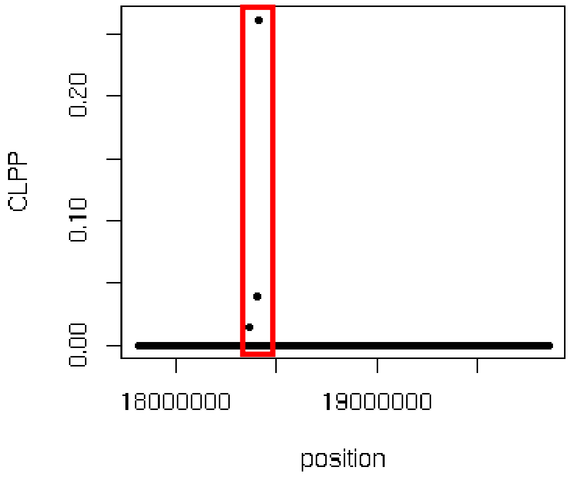
Strong correlation, CLPP = 0.26 for an intergenic variant near *BRD7*

colocalisation



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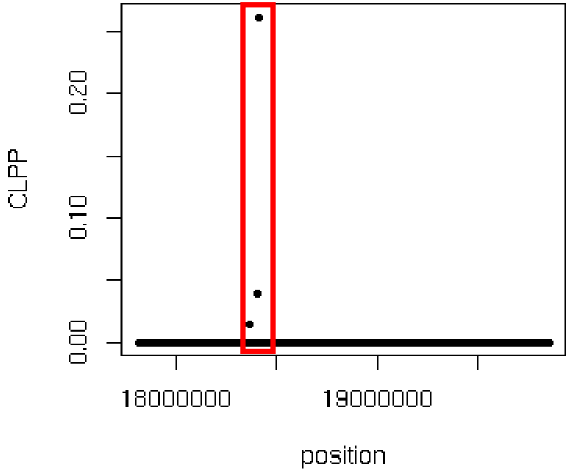
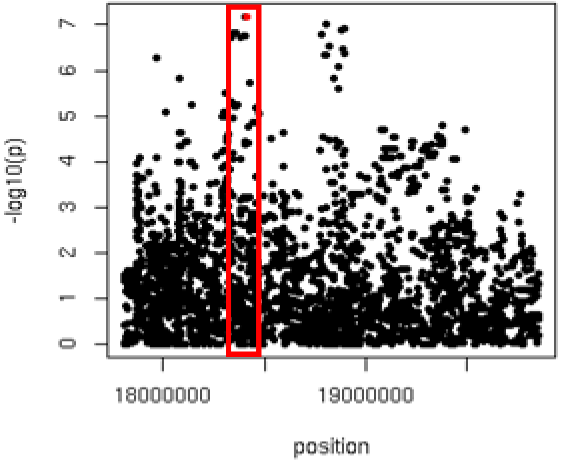
Strong correlation, CLPP = 0.26 for an intergenic variant near *BRD7*, top variant in eQTL


colocalisation


eQTL

Example: BRD7, chr 18, protein yield

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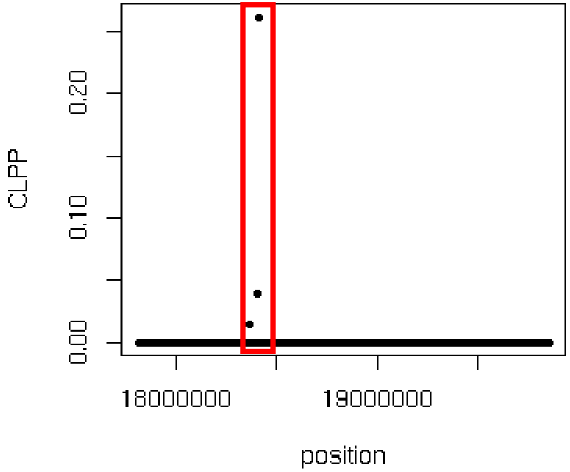
top variant in eQTL but not in GWAS

colocalisation



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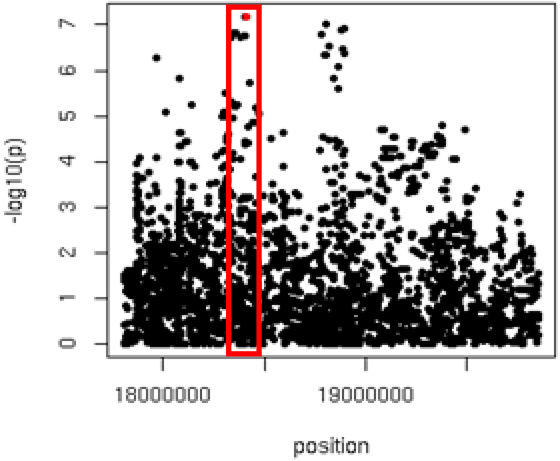
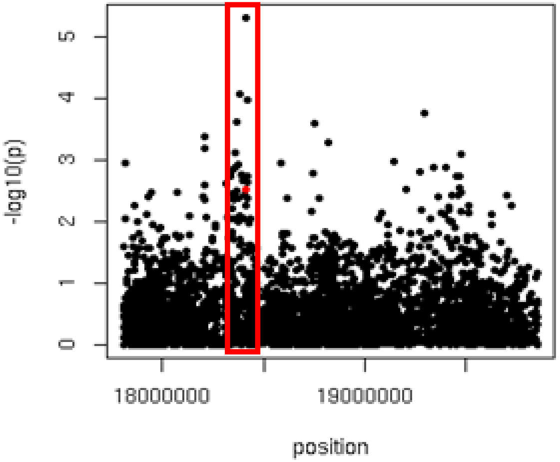


GWAS



Conclusions

- We found little overlap between QTL and eQTL

- Lack of power, need more powerful eQTL experiment?

- The QTL that we detected using expression data explained only a very small part of the total genetic variance

→ Expression data can help to identify small QTL, but in our study not enough of them to explain a substantial part of the total genetic variance

Acknowledgements

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DataGene
Solutions for Herd Development

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DairyBio