Sequence-based genome-wide association study of milk mid-infrared wavenumbers in dairy cattle

Kathryn Tiplady

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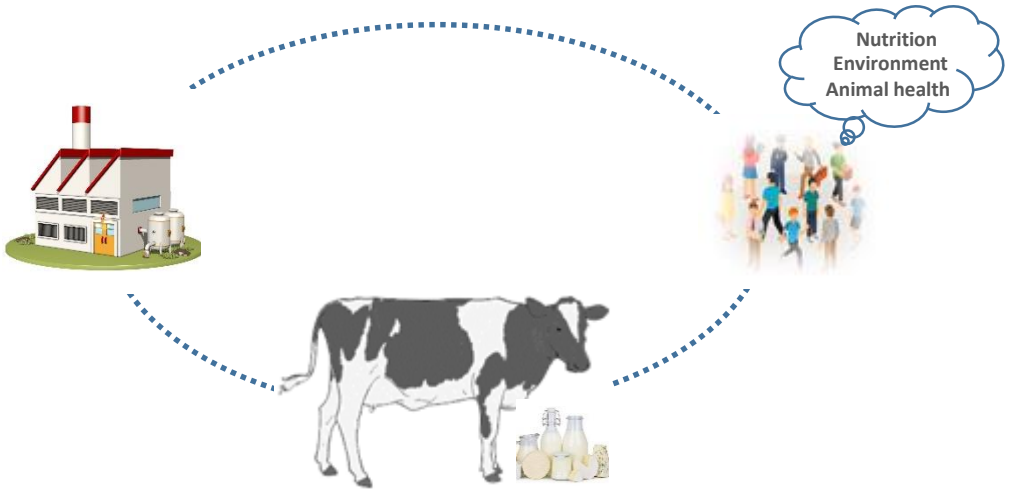
Introduction

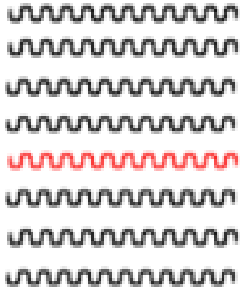
- Milk is highly complex.

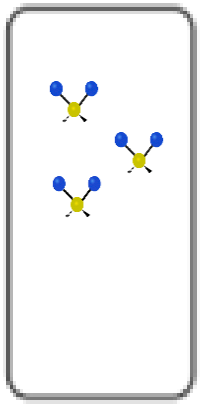


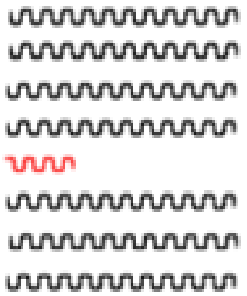
- Fourier-transform infrared (FTIR) spectroscopy is widely used to estimate milk composition and other indicator traits.
- High throughput, inexpensive, readily available from routine milk testing.

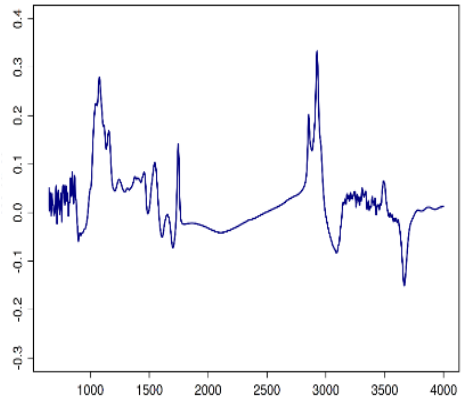
FTIR spectroscopy

Infrared light

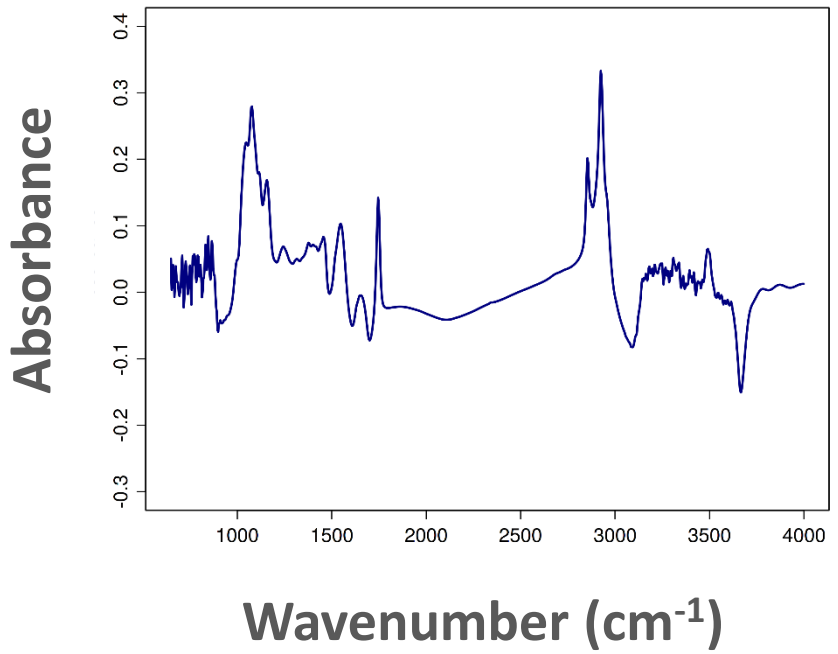








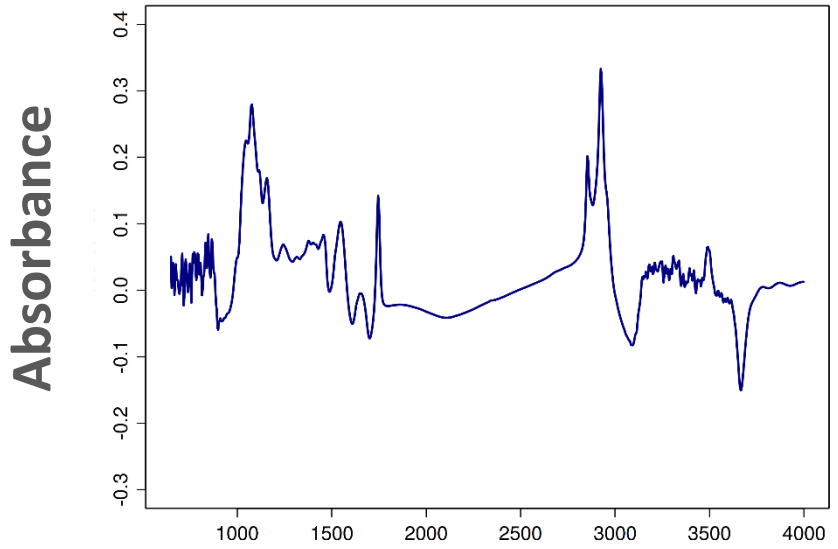
FTIR spectroscopy



$$Fat = F_0 + F_1 w_1 + F_2 w_2 + \cdots + F_k w_k$$

$$Protein = P_0 + P_1 w_1 + P_2 w_2 + \cdots + P_k w_k$$

FTIR spectroscopy



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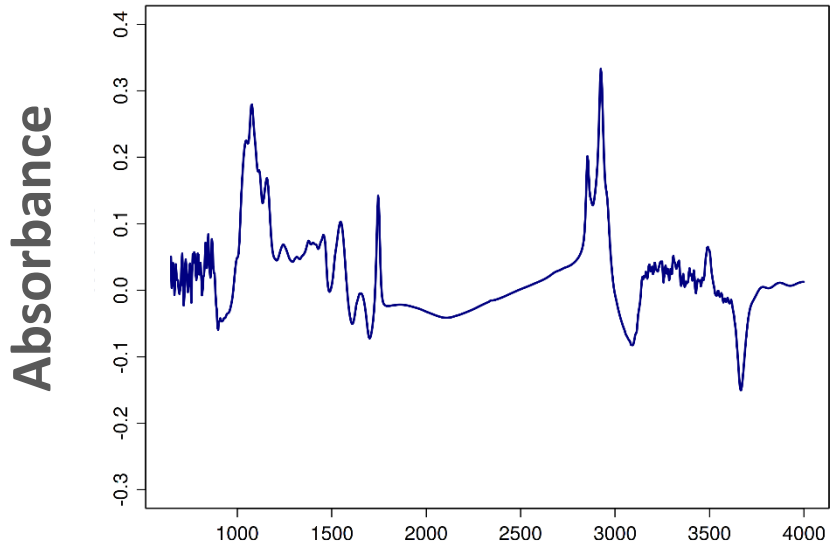
Energy balance
Fertility
Fatty acid profiles

Nitrogen
Methane

FTIR spectroscopy



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Energy balance
Fertility
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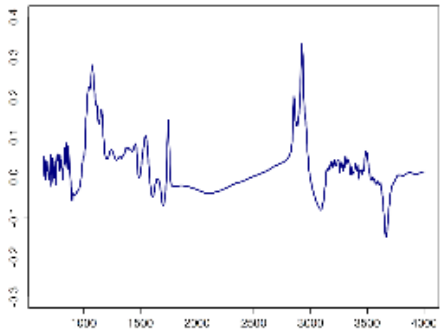
Genetics of FTIR data

- Individual wavenumbers have moderate to high heritability across the mid-infrared region (Bittante & Cecchinato 2013; Soyeurt et al. 2010).
- Some promising association peaks have been identified in other studies (Wang & Bovenhuis 2018; Bendet et al. 2019).

Aim of our study

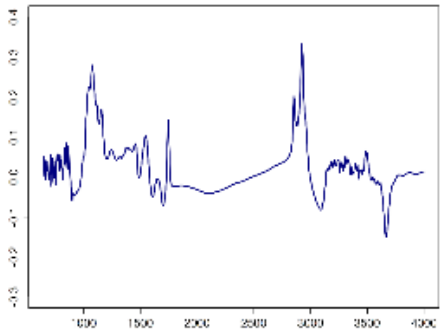
- Identify associations between individual mid-infrared wavenumbers and regions of the genome.

Identify genomic associations



GWAS

Identify genomic associations



GWAS

Dataset

- 100,671 FTIR records: 38,085 mixed-breed NZ dairy cattle.
- Imputed sequence: 17,776,293 variants.
- Individual wavenumbers standardized (Grelet et al., 2015; Tiplady et al., 2019).
- Adjusted for parity, days in milk, breed, heterosis and herd by test date (ASReml mixed linear model).

Identify genomic associations

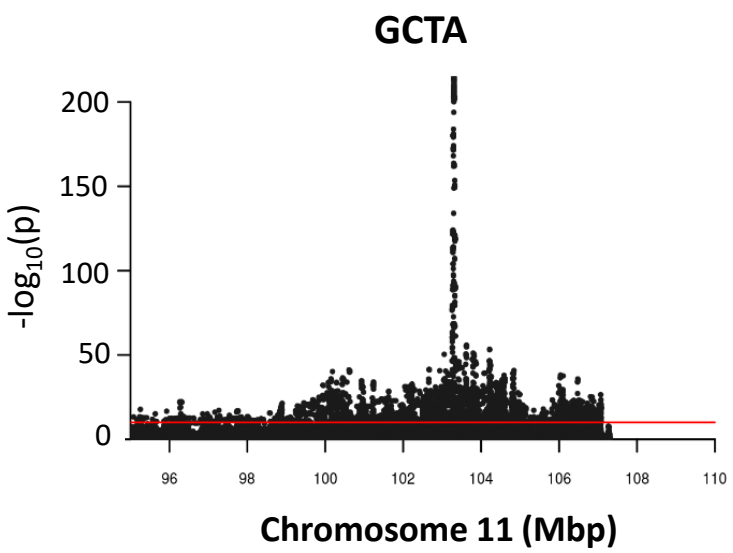
Sequence-based GWAS: ~38k animals, ~17.7m variants, 895 traits

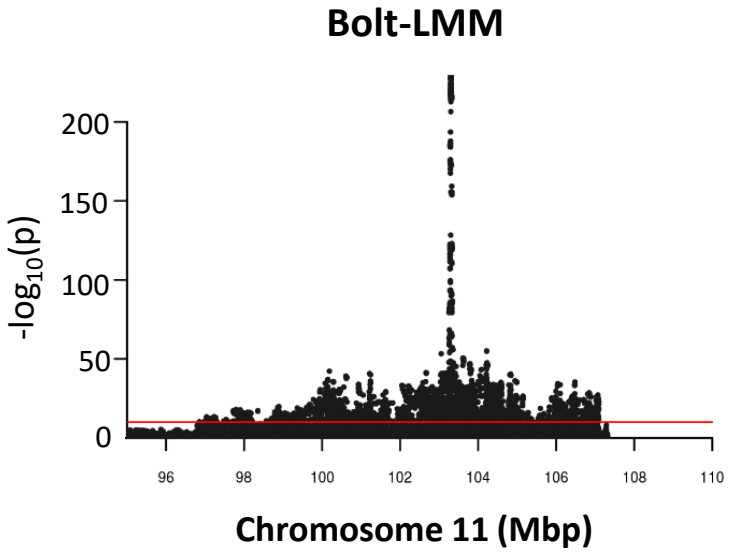
Computation challenges

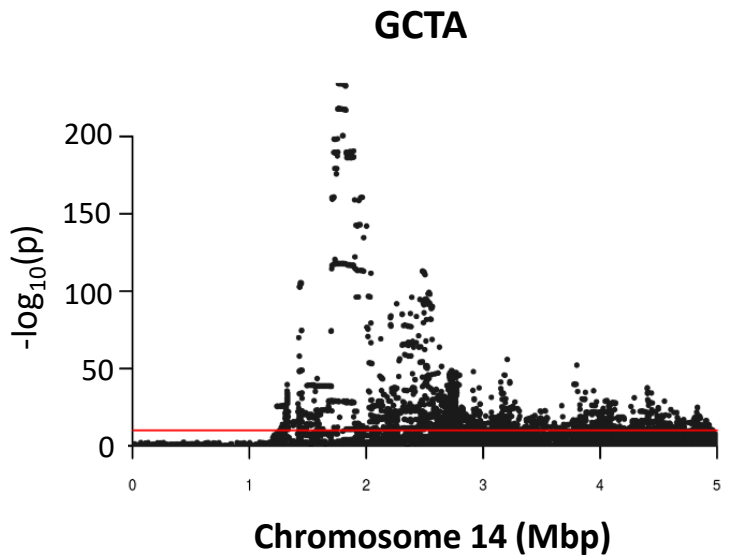
- GCTA (Yang et al., 2011): 1800 hours per trait ⇨ ~ 6 years
- Bolt-LMM (Loh et al., 2015): 6 hours per trait ⇨ ~ 7 days

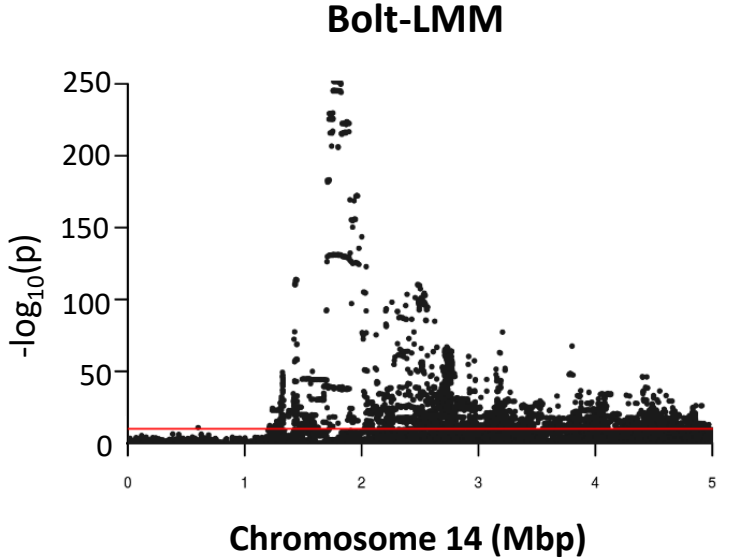
- Comparisons made using 43,851 SNP to account for population stratification.

Software comparisons





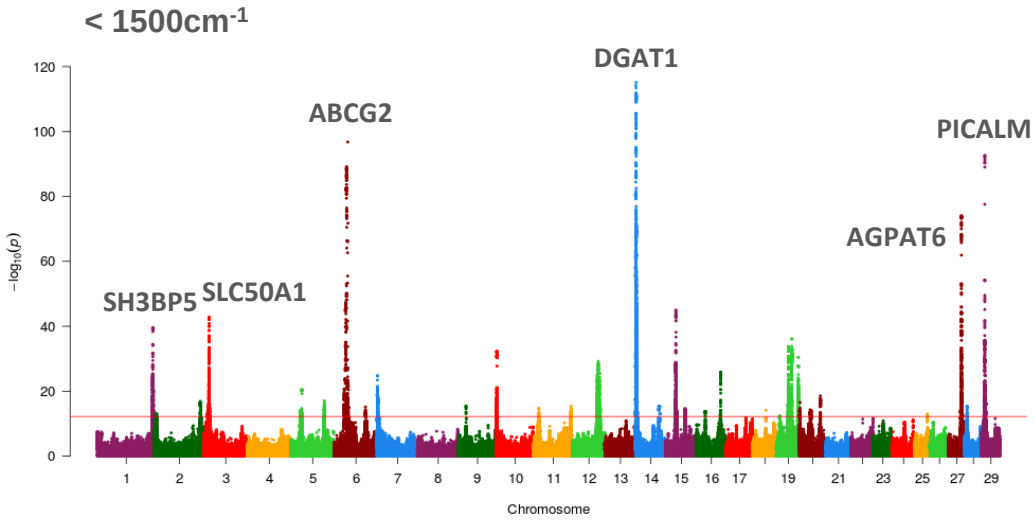


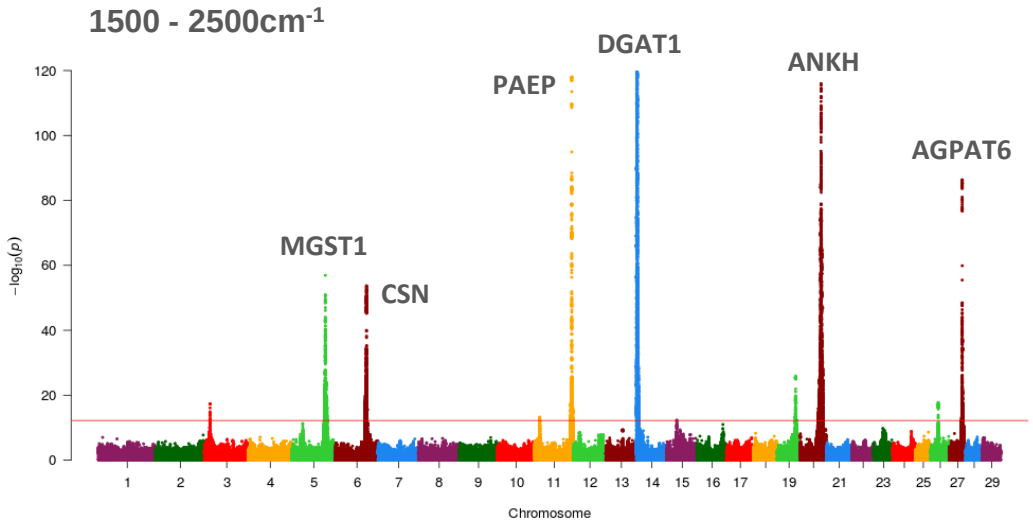


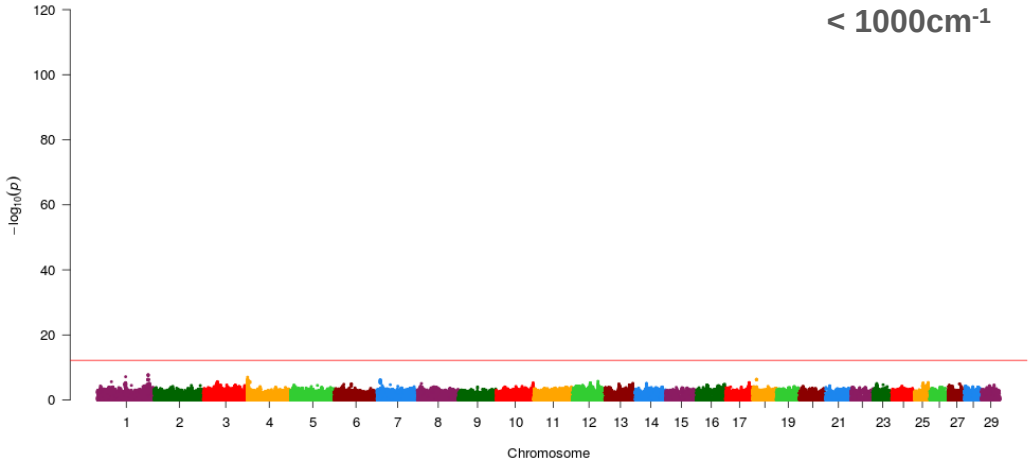
~1800 hours/trait

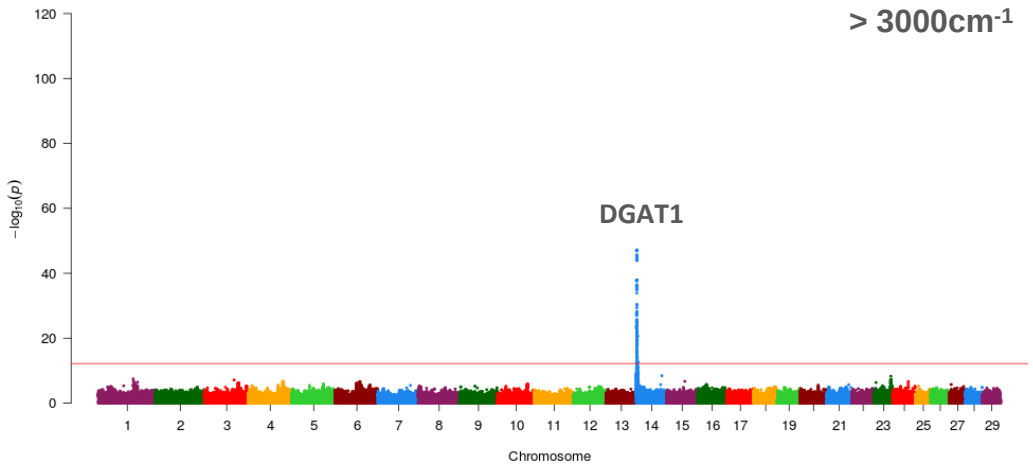
~6 hours/trait

Results







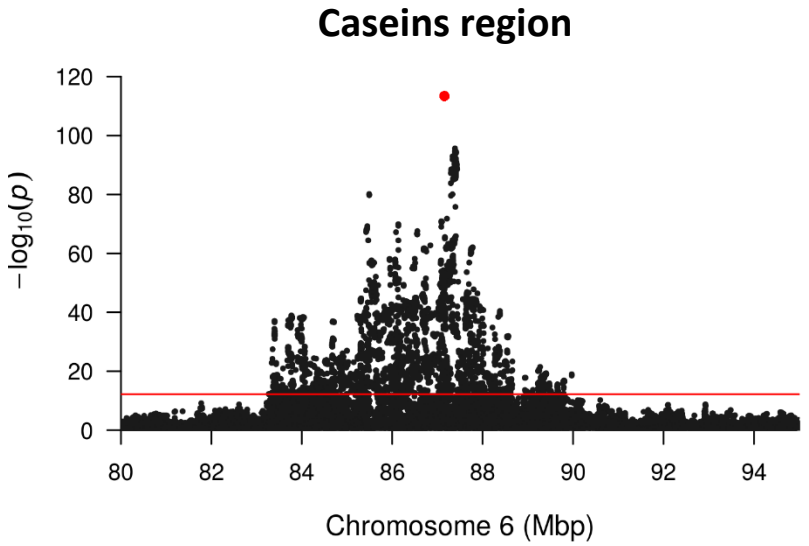


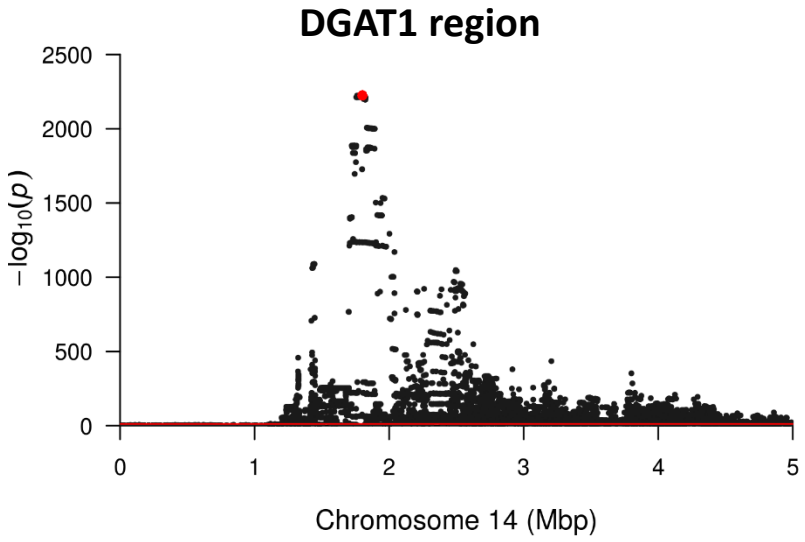
Bonferroni-threshold: $0.01/17.7m/895=6.3 \times 10^{-13}$.

Significant associations conserved across multiple wavenumbers: DGAT1 significant for over 750 wavenumbers!

Peak identification

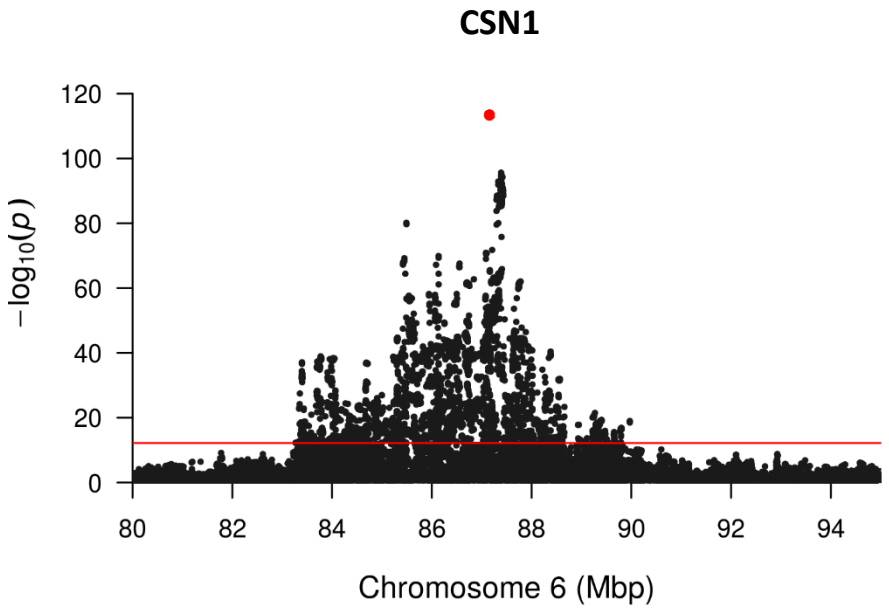
- How to deal with complex regions?
  e.g: Caseins region on BTA6; DGAT1 region at the start of BTA14.

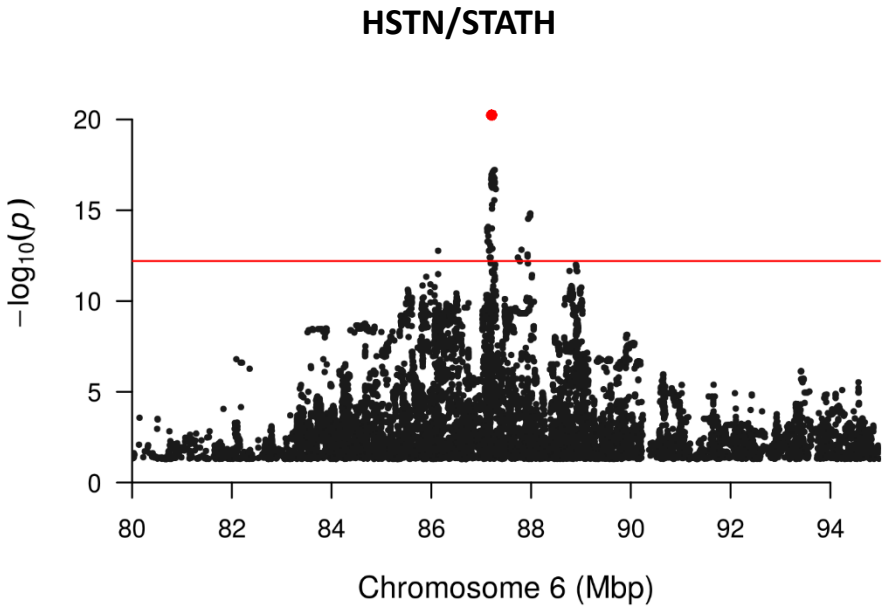


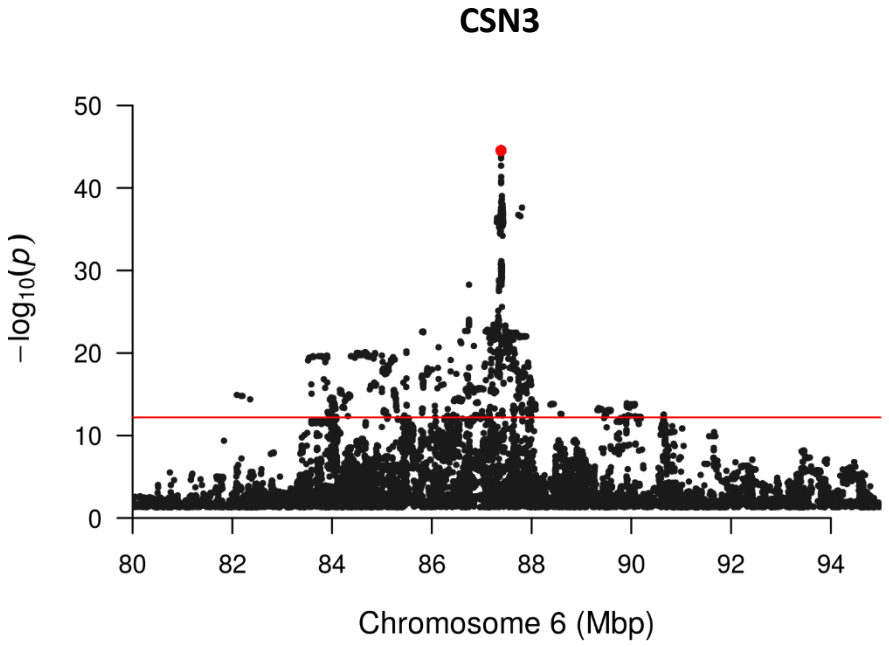


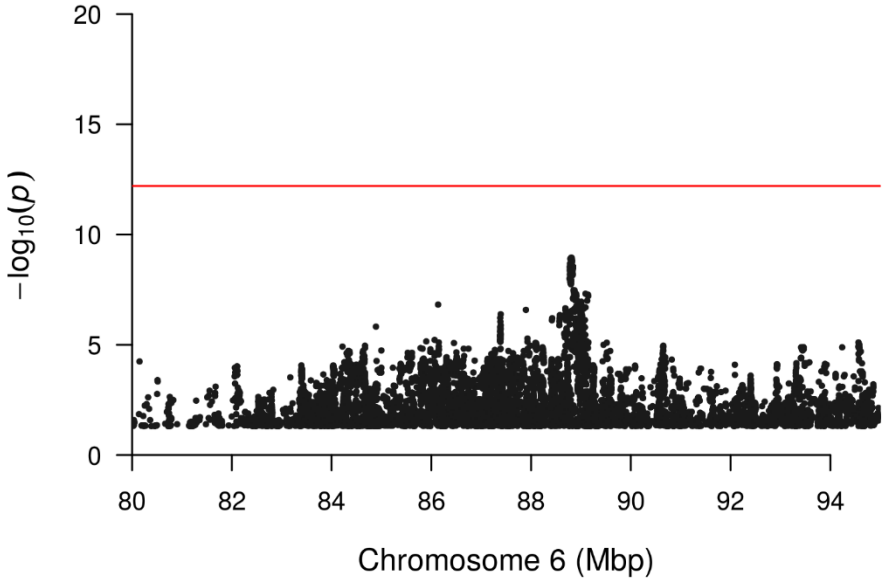
- Conditional iterative GWAS for each wavenumber.
  - Top SNP on each chromosome fitted as a covariate.
  - Iteratively run until there no signal left.

Peak identification









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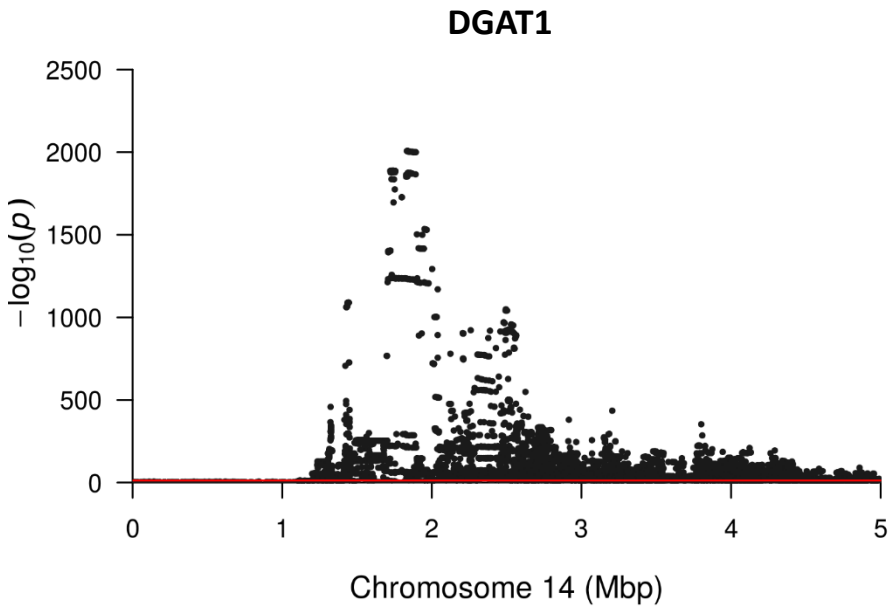
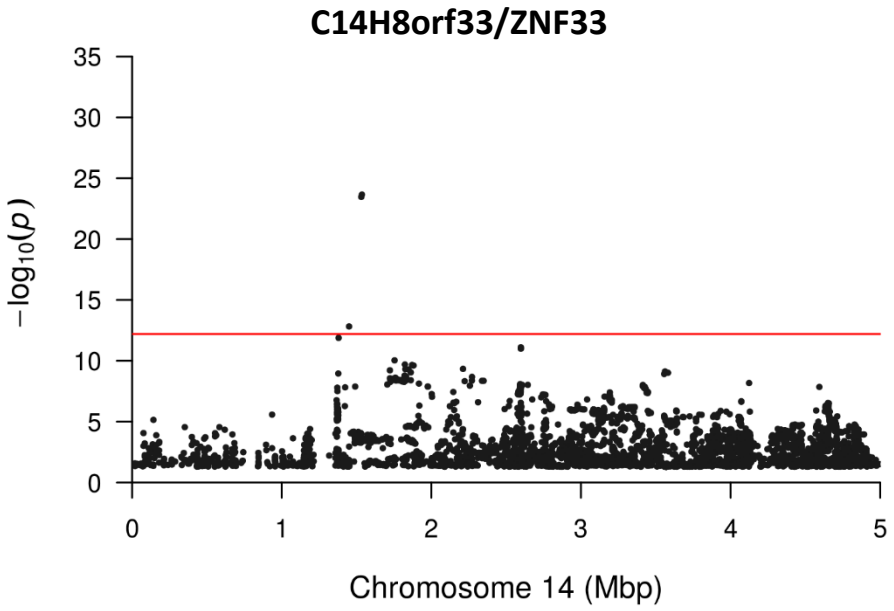
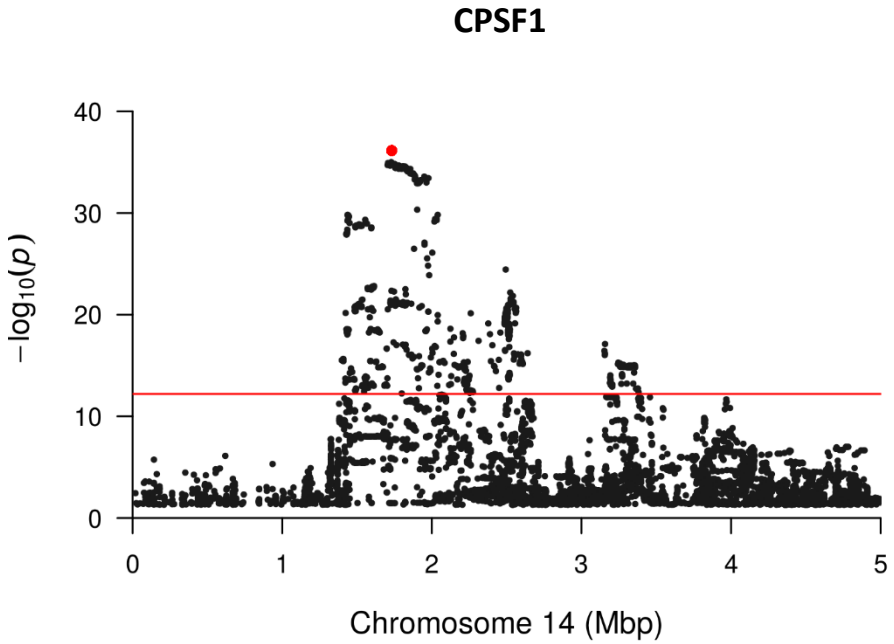
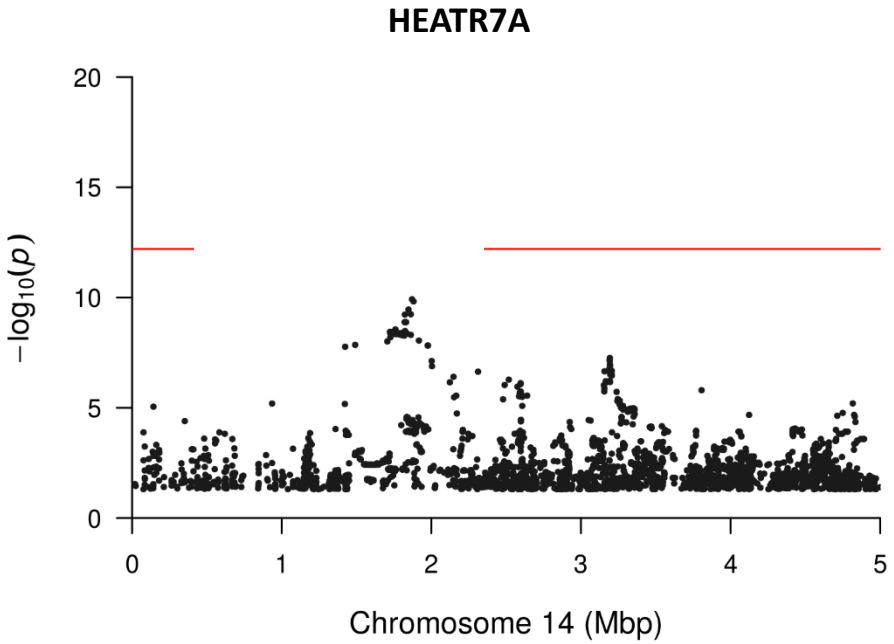


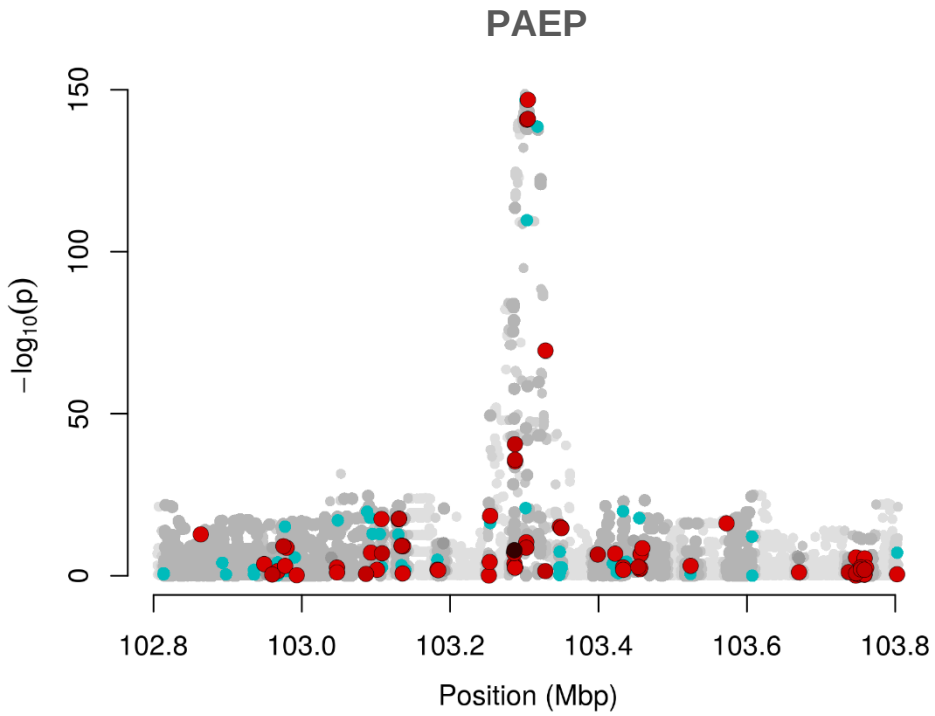


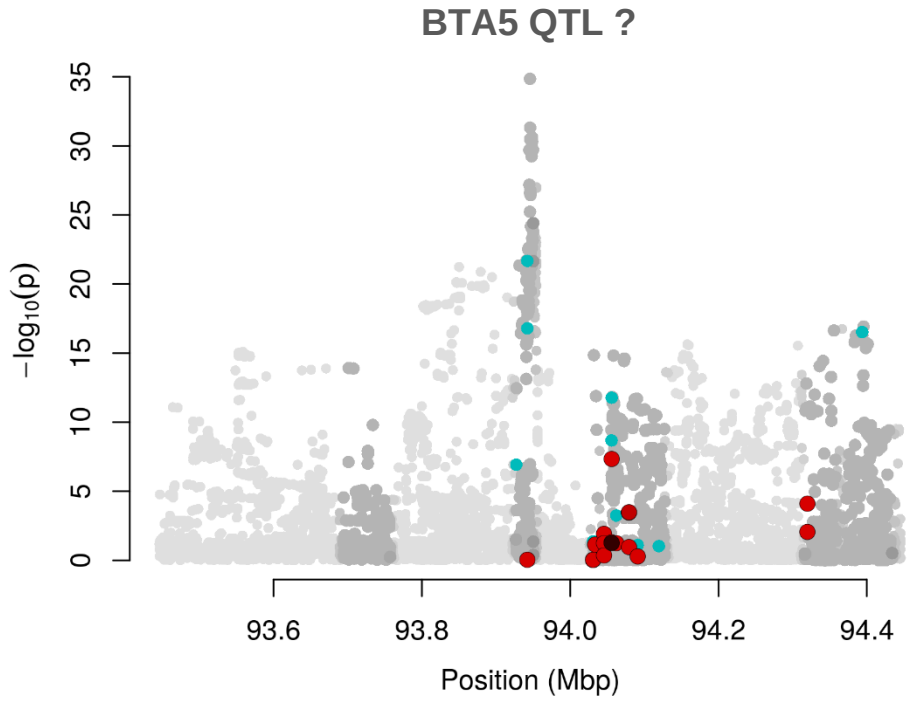




Determine likely candidates

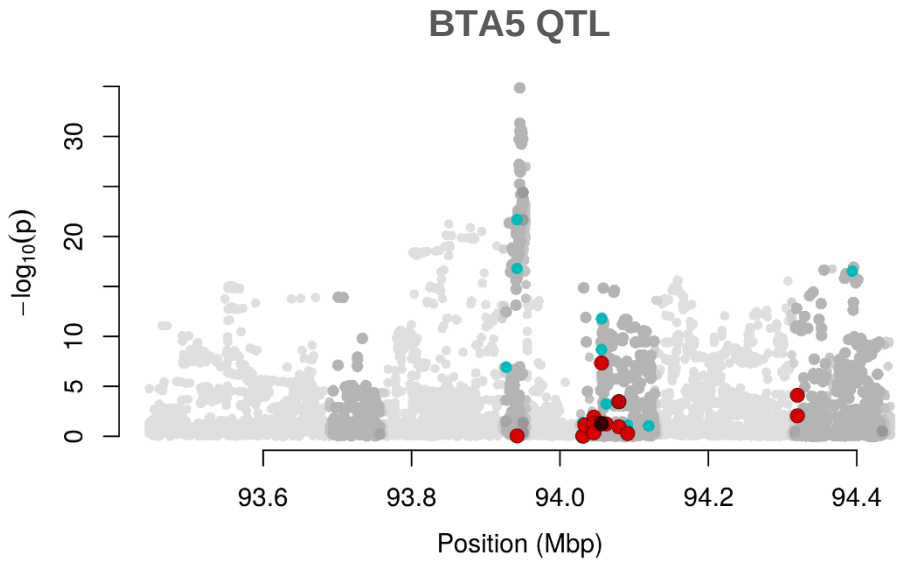
Link associations to SnpEff annotation - assess the candidacy of variants in terms of their predicted impact on protein sequence.





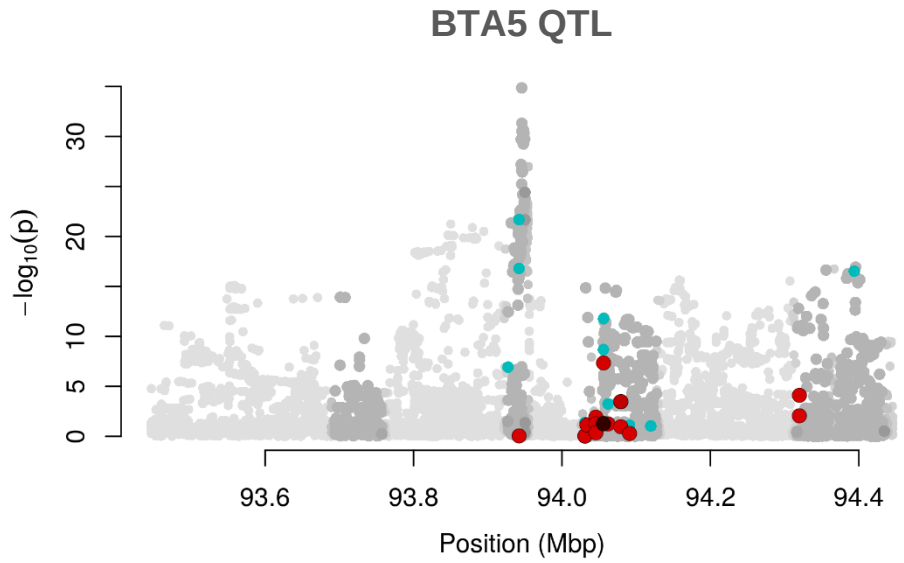
- High impact: Slice donor/acceptor, frameshift variants
- Moderate: Missense, splice region variants
- Low impact: Synonymous variants, non-coding exons
- Modifiers: Intron and up/downstream variants, UTRs.

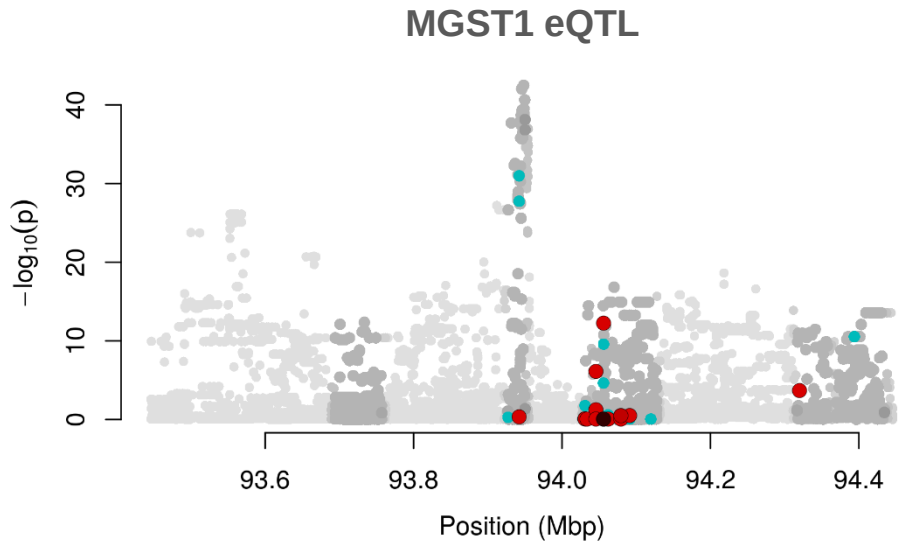
Co-locating eQTLs



- Gene expression data from mammary tissue in 375 animals (Lopdell et al., 2017).
- A co-locating eQTL indicates genetic regulation of the gene in the same region that we see the trait QTL.

Co-locating eQTLs





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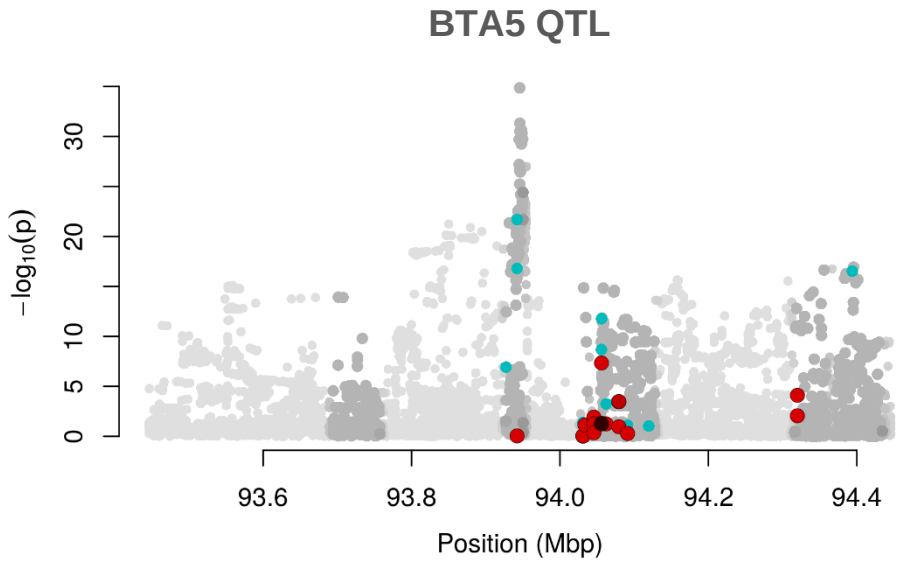

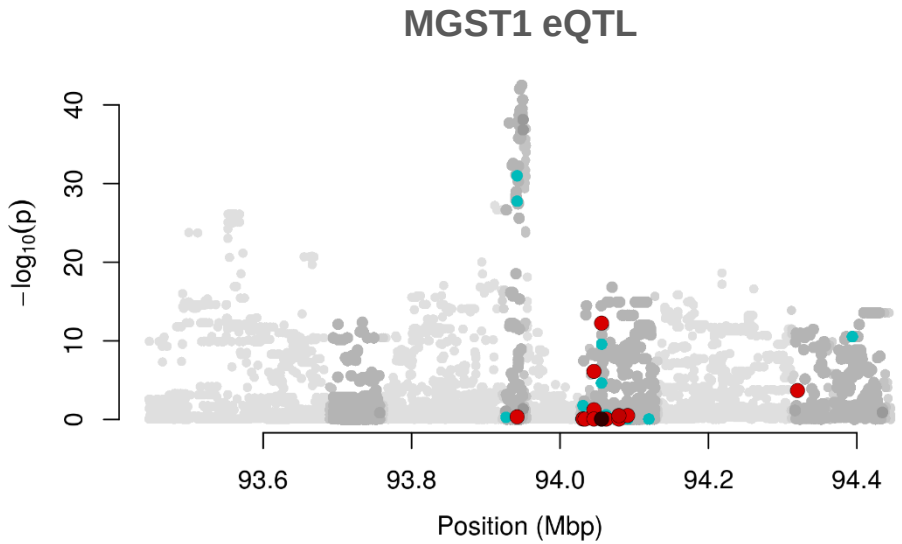

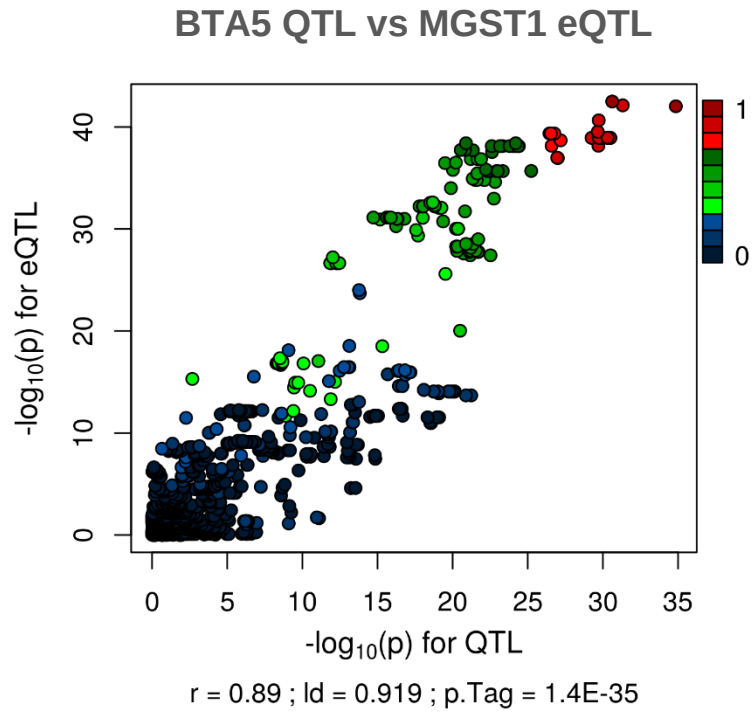

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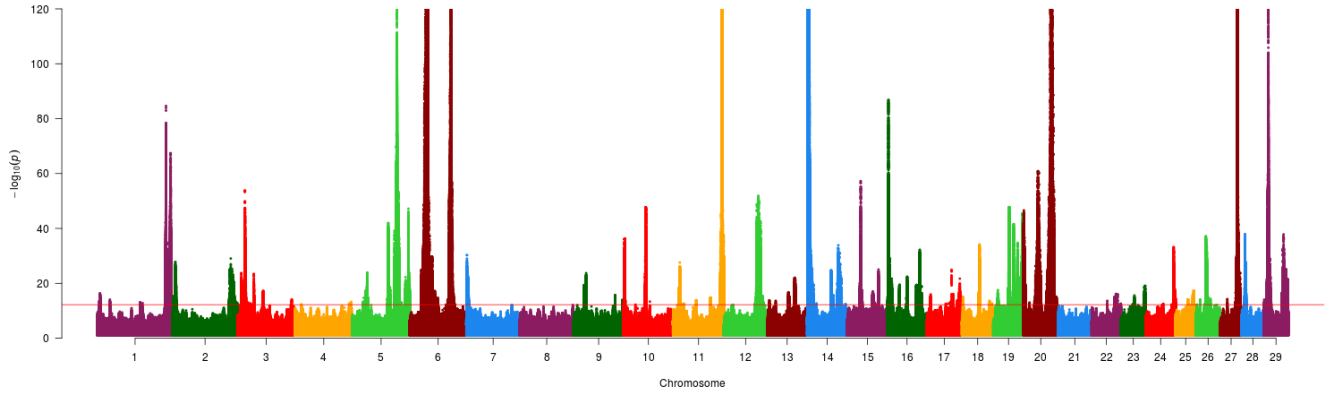
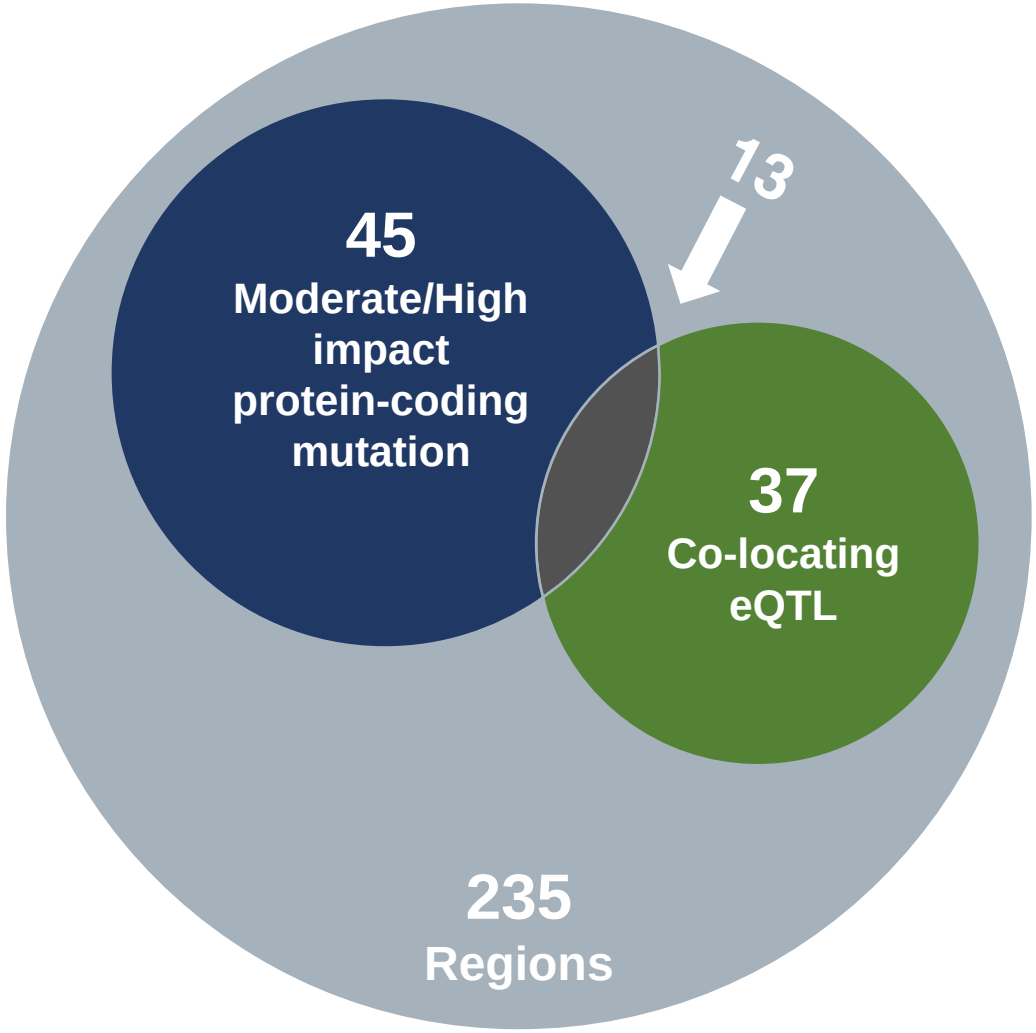
Peak overview





Summary

- GWAS on mid-infrared wavenumbers conducted
  - Bolt-LMM: ~38k animals, ~17.7m variants, 895 traits
  - Multiple QTL in complex regions ⇨ Conditional iterations.

- Promising peaks with candidate variants and co-locating eQTLs identified.
- Ongoing research to consolidate results and determine how we can use this information to improve genomic selection.

Acknowledgements

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Hugh Blair (Massey)

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