Dissecting and fine-mapping *trans*-eQTL hotspots

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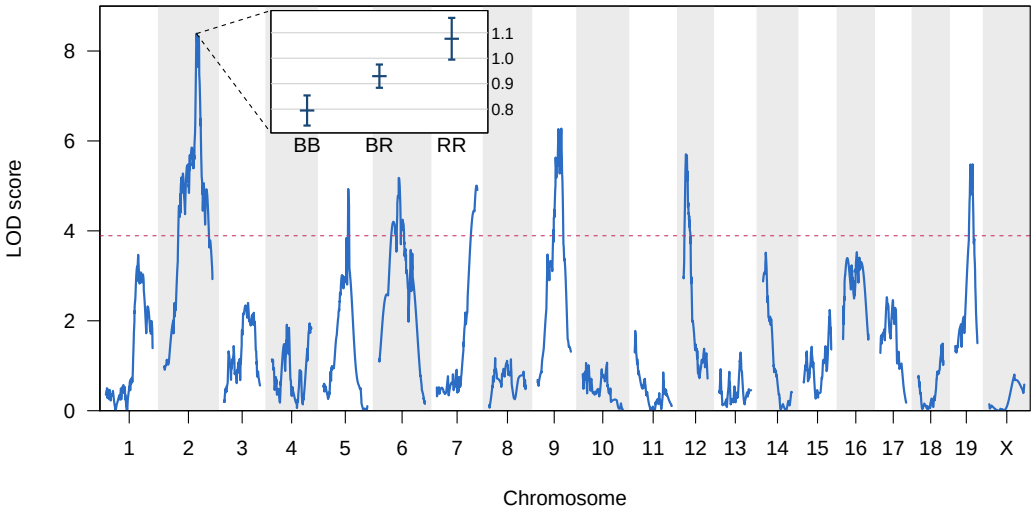
QTL mapping

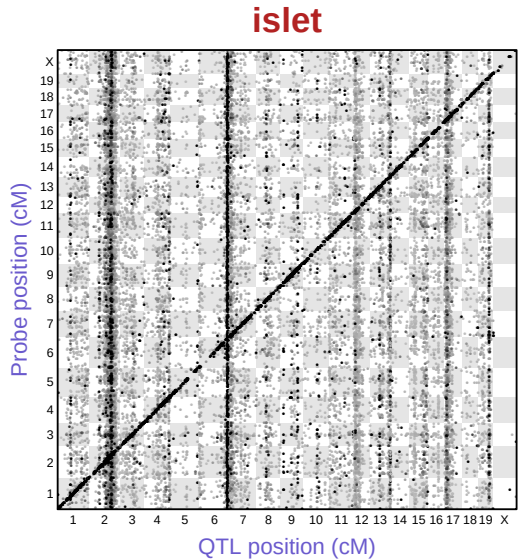

LOD score
0
2
4
6
8
1
2
3
4
5
6
7
8
9
10
11
12
13
14
15
16
17
18
19
X
Chromosome
1.1
1.0
0.9
0.8
BB
BR
RR

DNA $\longrightarrow$ RNA $\longrightarrow$ protein

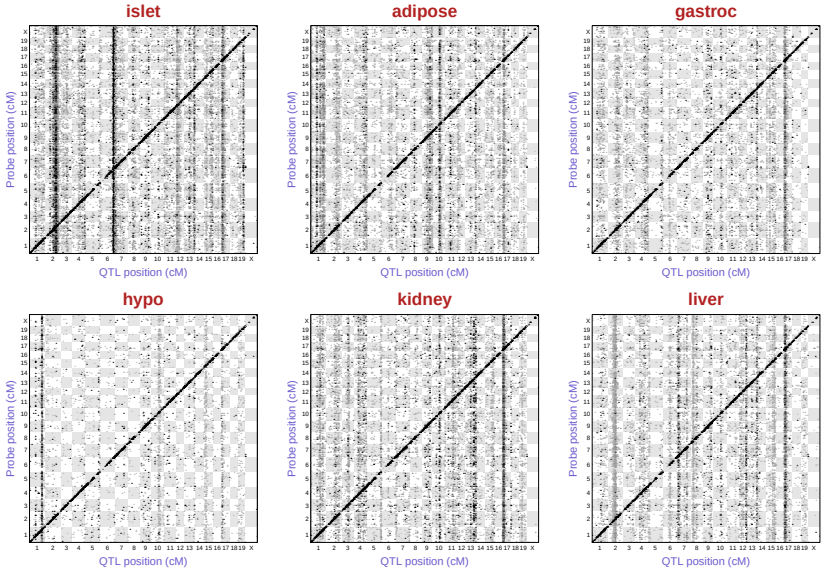
DNA $\longrightarrow$ RNA $\longrightarrow$ protein $\longrightarrow$ phenotype

Gene expression microarrays

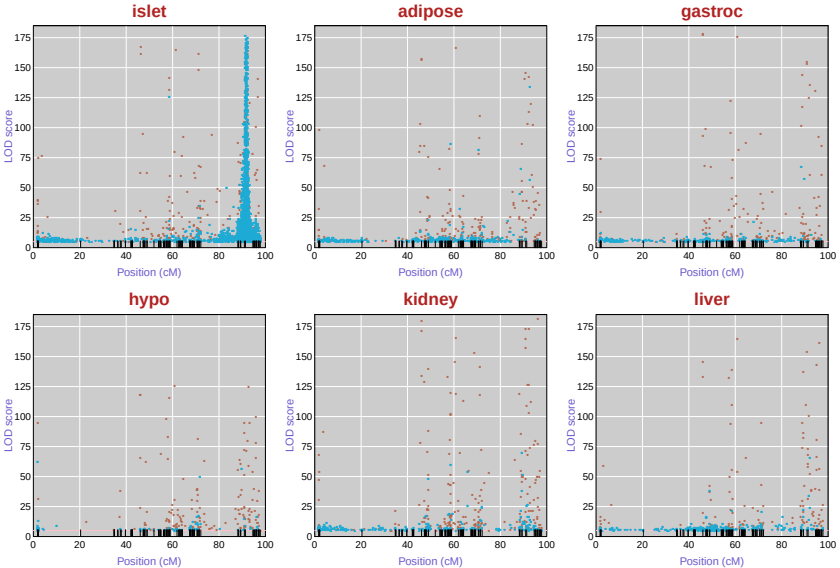
eQTL results



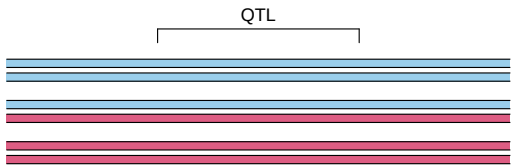
eQTL results



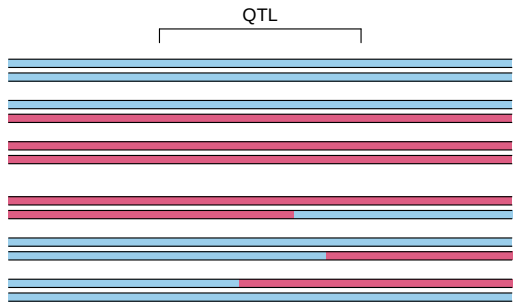
Chr 6


islet
adipose
gastroc
hypo
kidney
liver
LOD score
Position (cM)
0
25
50
75
100
125
150
175
0
20
40
60
80
100

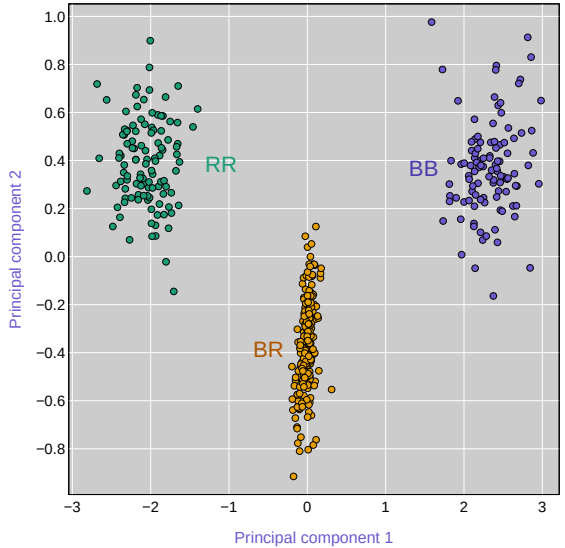
Consider the non-recombinants…



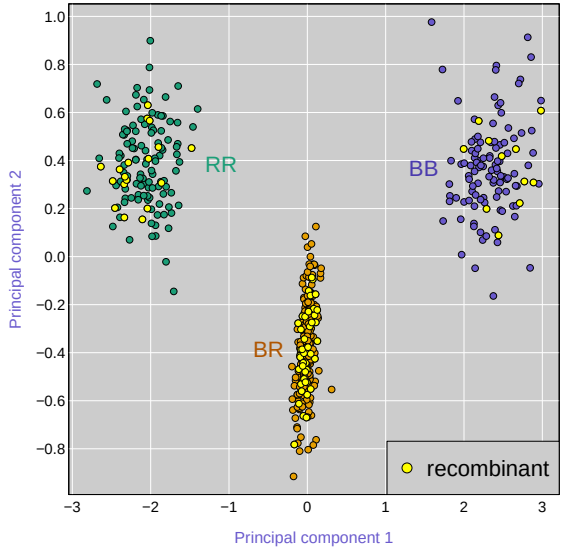
Consider the non-recombinants…



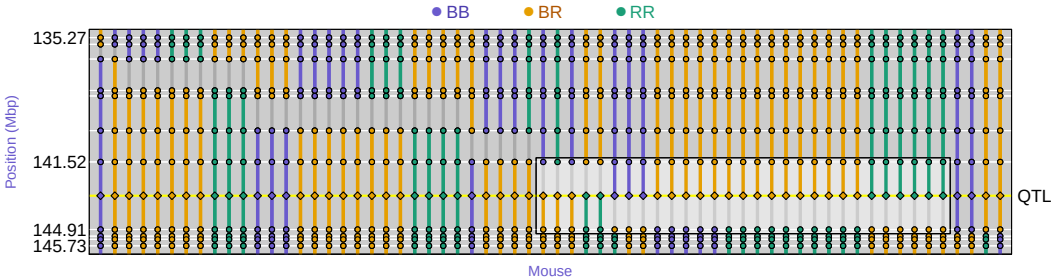
Islet c6 PCs


RR
BB
BR
Principal component 2
Principal component 1
1.0
0.8
0.6
0.4
0.2
0.0
−0.2
−0.4
−0.6
−0.8
−3
−2
−1
0
1
2
3

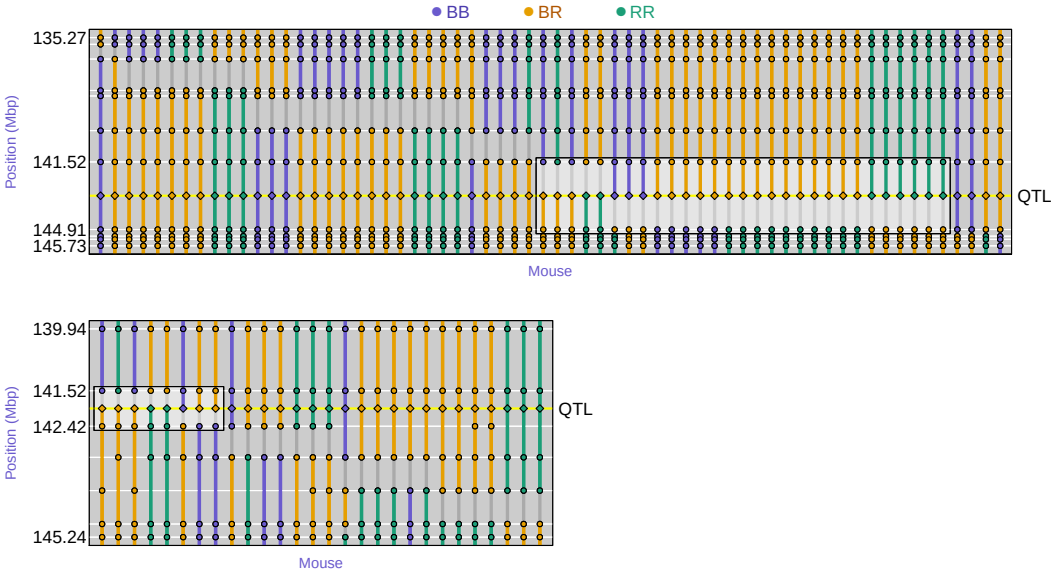
Islet c6 PCs


RR
BB
BR
recombinant
Principal component 2
Principal component 1
1.0
0.8
0.6
0.4
0.2
0.0
−0.2
−0.4
−0.6
−0.8
−3
−2
−1
0
1
2
3

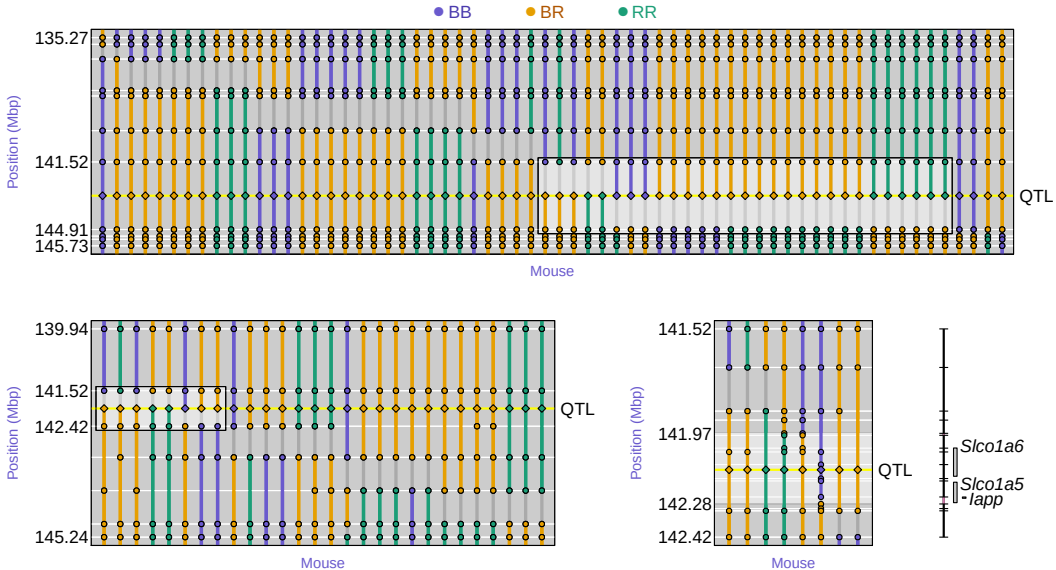
Fine-mapping the c6 locus



Fine-mapping the c6 locus

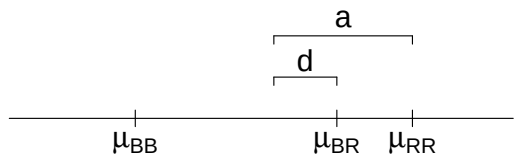


Fine-mapping the c6 locus

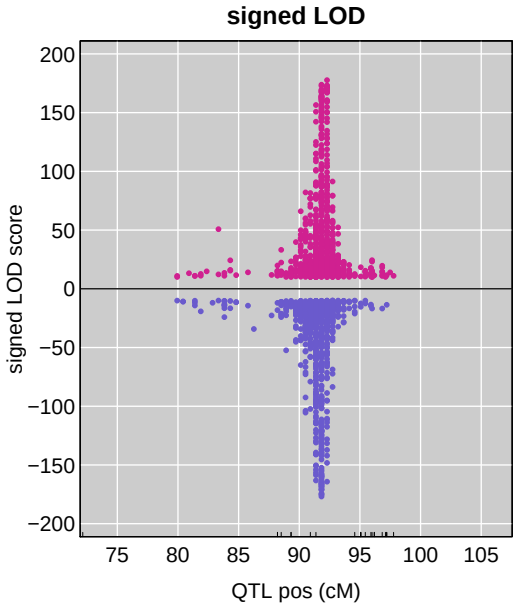


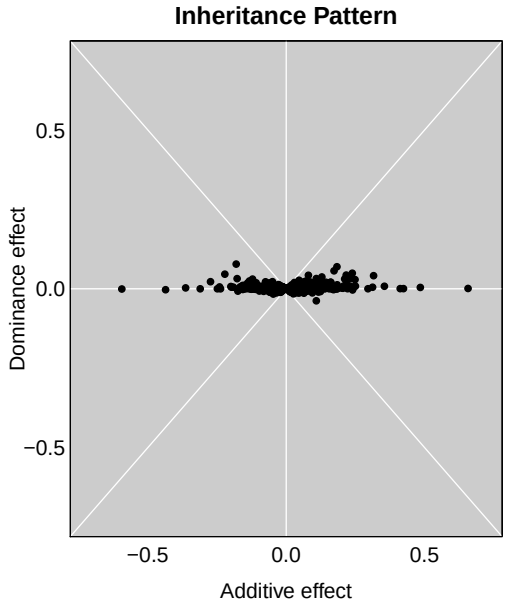
Is it one QTL?

Consider the QTL effects…

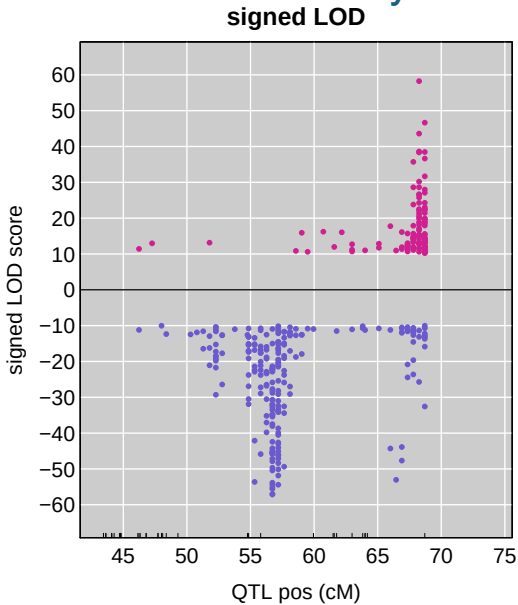


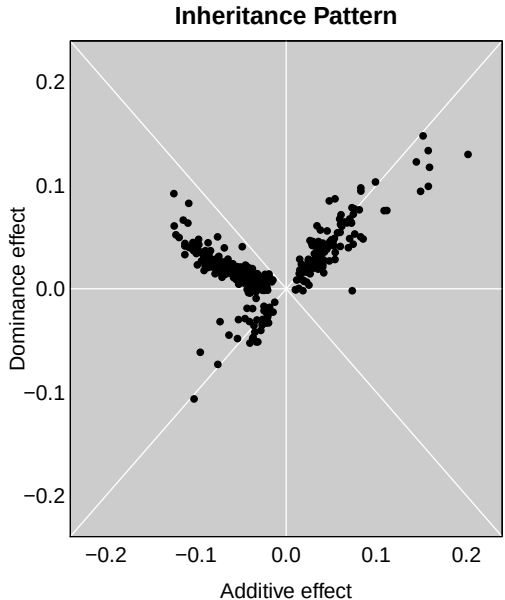
eQTL effects: Islet c6



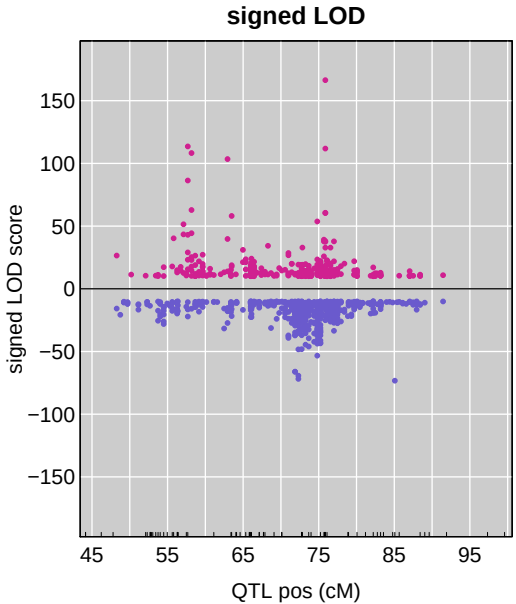


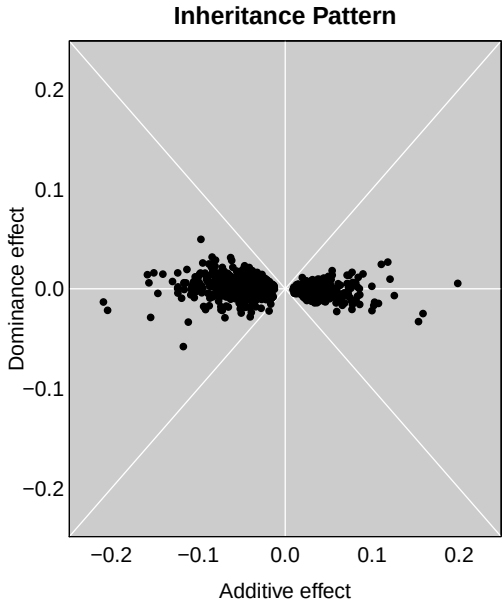
eQTL effects: Kidney c13



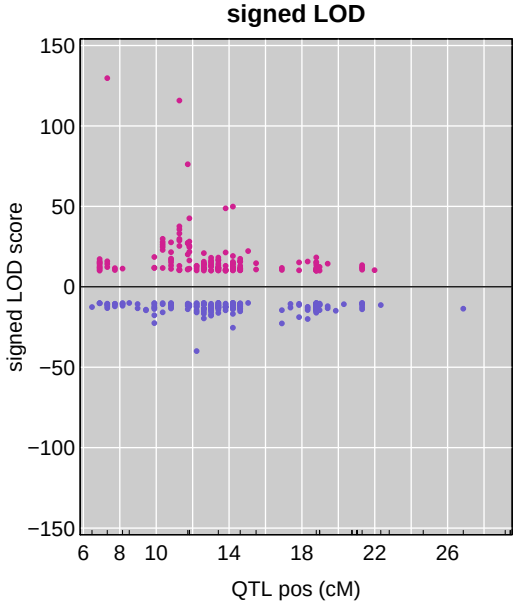


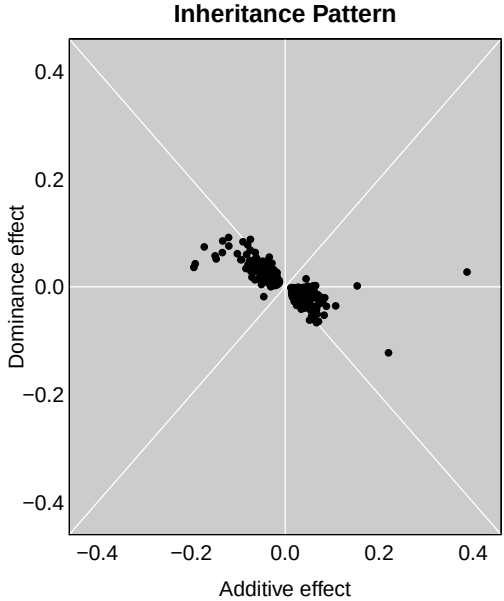
eQTL effects: Islet c2



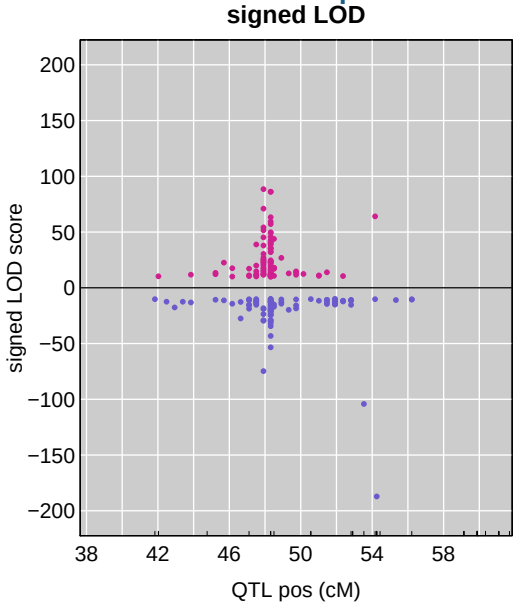


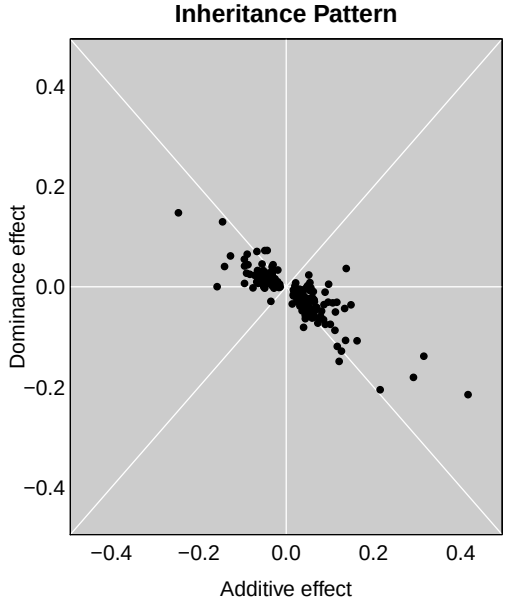
eQTL effects: Liver c17





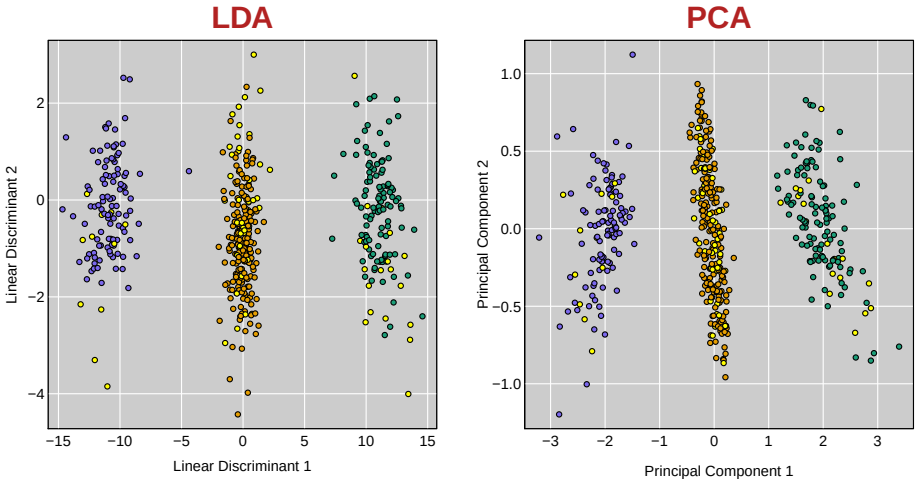
eQTL effects: Adipose c10



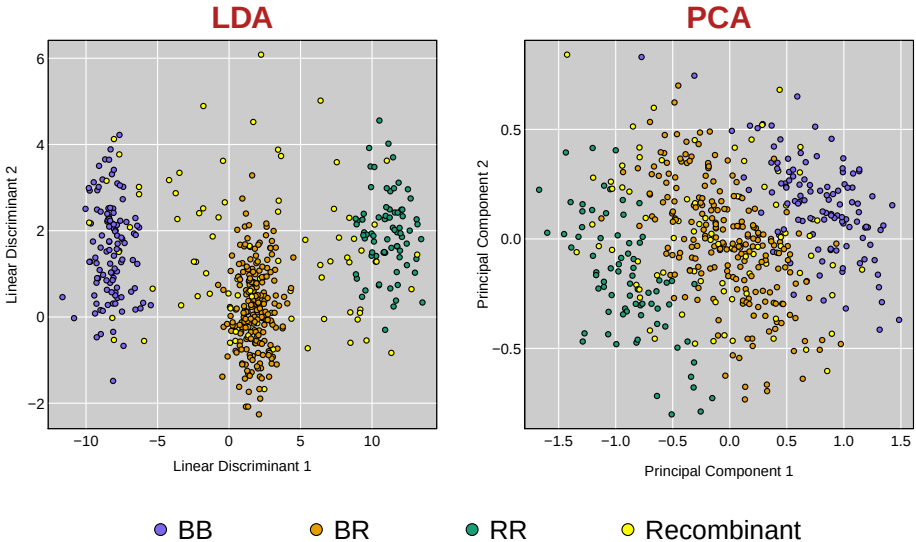


Compare the recombinants and non-recombinants.

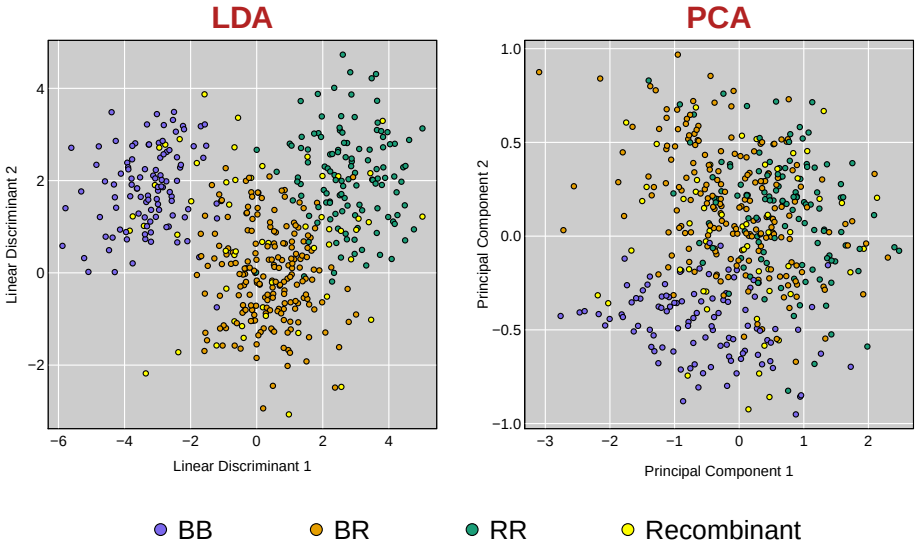
LDA & PCA: Islet c6



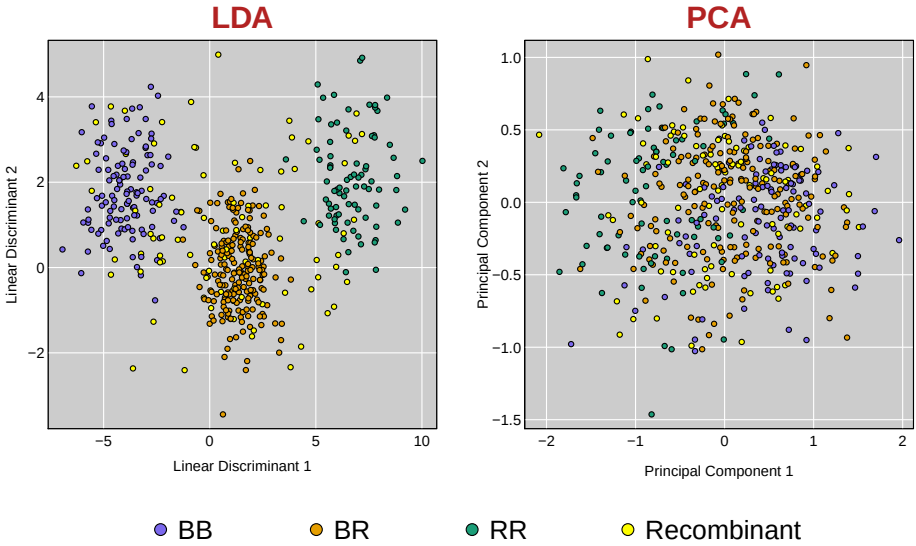
LDA & PCA: Islet c2



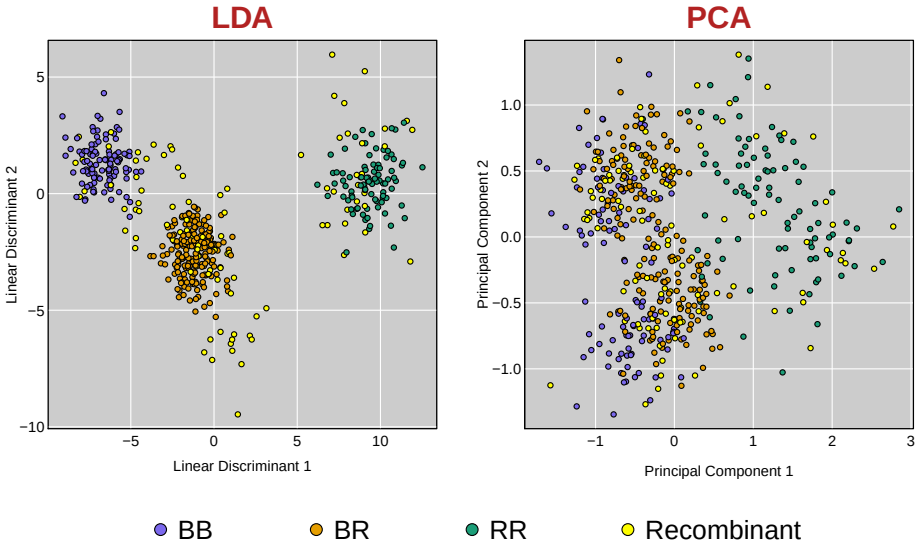
LDA & PCA: Kidney c13



LDA & PCA: Liver c17



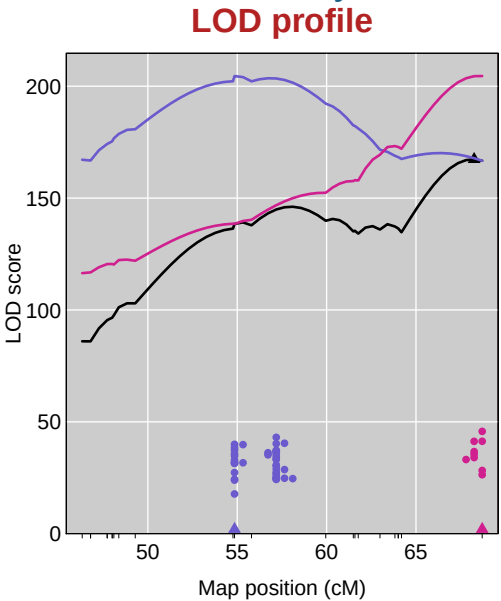
LDA & PCA: Adipose c10

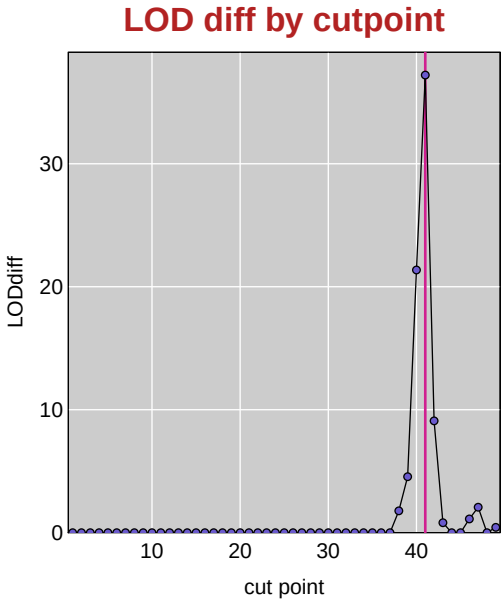


Formal test for 1 vs 2 QTL

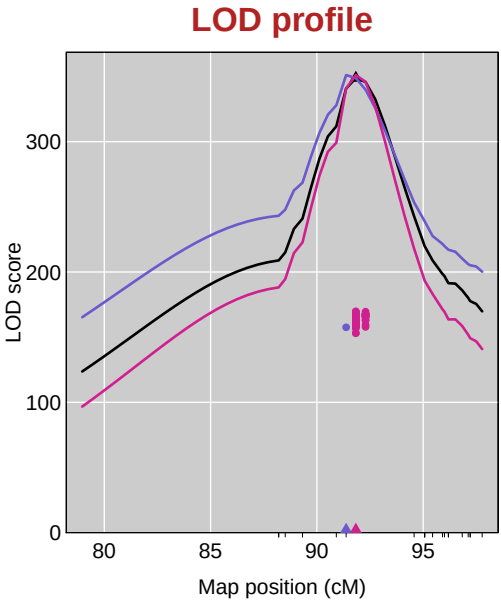
- Consider a set of traits mapping to common eQTL
- Multivariate QTL analysis with 1 or 2 QTL
- With 2-QTL model, each trait affected by one or the other QTL
  - Order traits by estimated QTL location when considered separately
  - Consider cut points of the list, assign first group to one QTL and second group to other.
- P-value: parametric bootstrap or stratified permutation

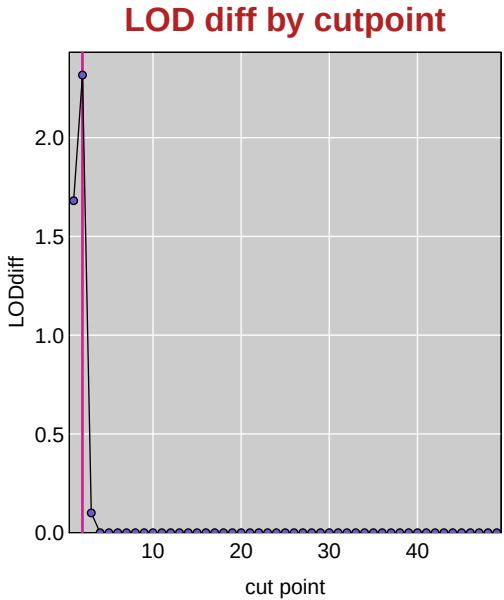
1 vs 2 QTL: Kidney c13





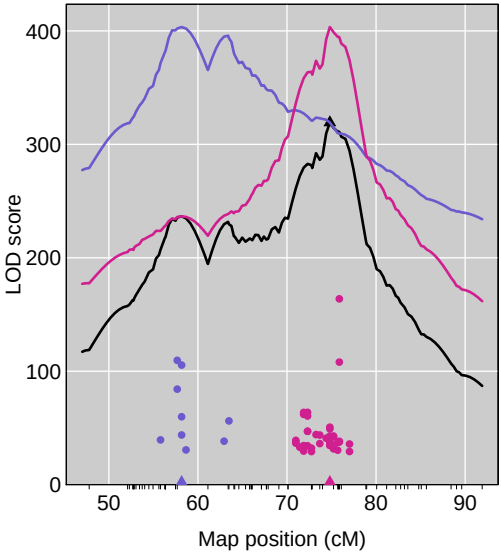
1 vs 2 QTL: Islet c6



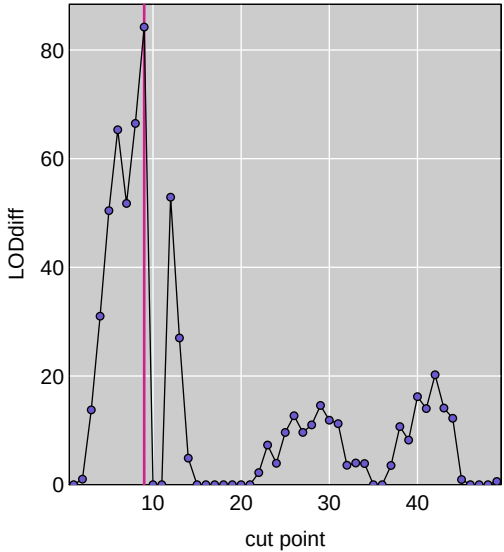


1 vs 2 QTL: Islet c2

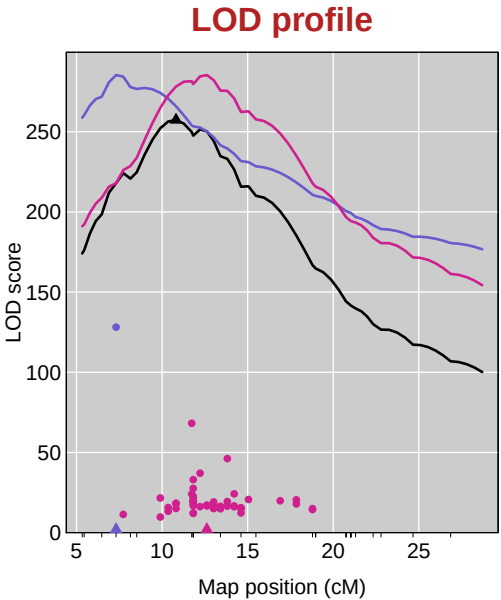
LOD profile

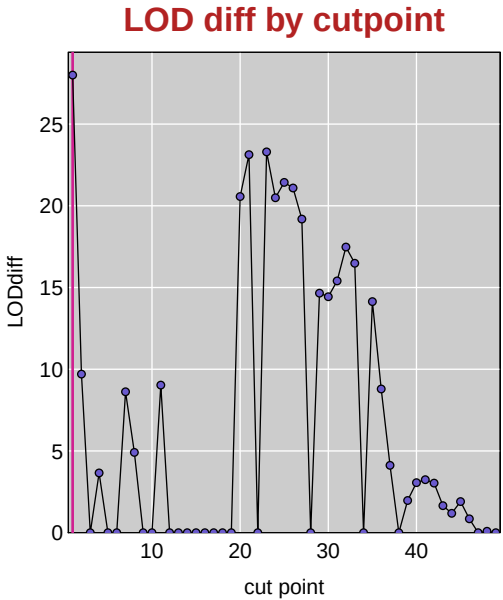


LOD diff by cutpoint



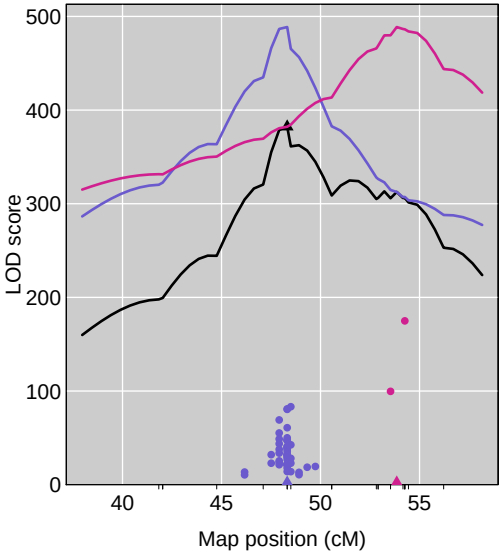
1 vs 2 QTL: Liver c17



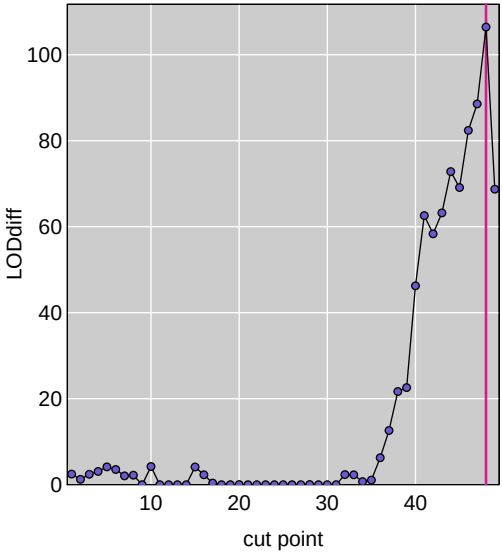


1 vs 2 QTL: Adipose c10

LOD profile



LOD diff by cutpoint



Summary

- Fine-mapping a *trans*-eQTL hotspot
  - Consider the non-recombinants
  - Predict QTL genotype of recombinants
    $\longrightarrow$ Mendelian trait
  - Fine-map by traditional means
- Large-effect locus on chr 6
  - Affects expression of $\sim$8% of genes
  - Effects specific to pancreatic islets
  - Looks to be *Slco1a6*
- Dissecting a *trans*-eQTL hotspot
  - Sign of eQTL effect
  - Degree of dominance
  - Compare recombinants and non-recombinants
  - Formal statistical test

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Wen Zhao

Merck & Co., Inc.

Amit Kulkarni

Mt. Sinai

Eric Schadt

NIH: R01 GM074244, R01 DK066369

References

- Tian J et al. (2015) Identification of the bile acid transporter *Slco1a6* as a candidate gene that broadly affects gene expression in mouse pancreatic islets. *Genetics* 201:1253–1262
  doi:10.1534/genetics.115.179432
- Tian J et al. (2016) The dissection of expression quantitative trait locus hotspots. *Genetics* 202:1563–1574
  doi:10.1534/genetics.115.183624