

Dissecting and fine-mapping *trans*-eQTL hotspots

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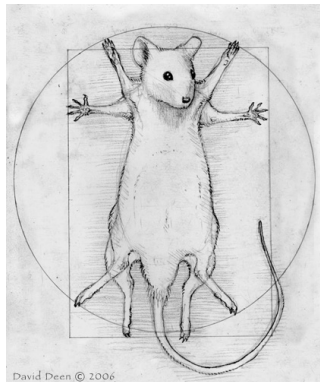
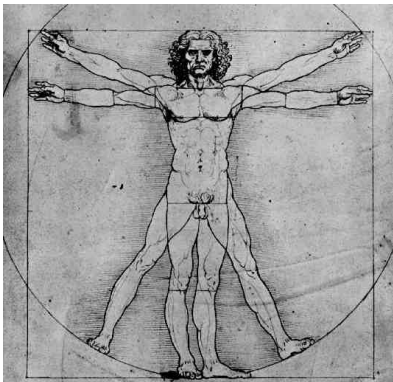
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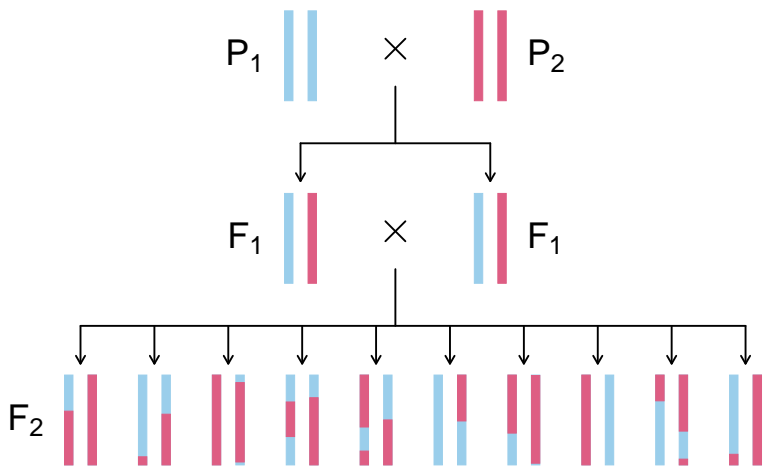




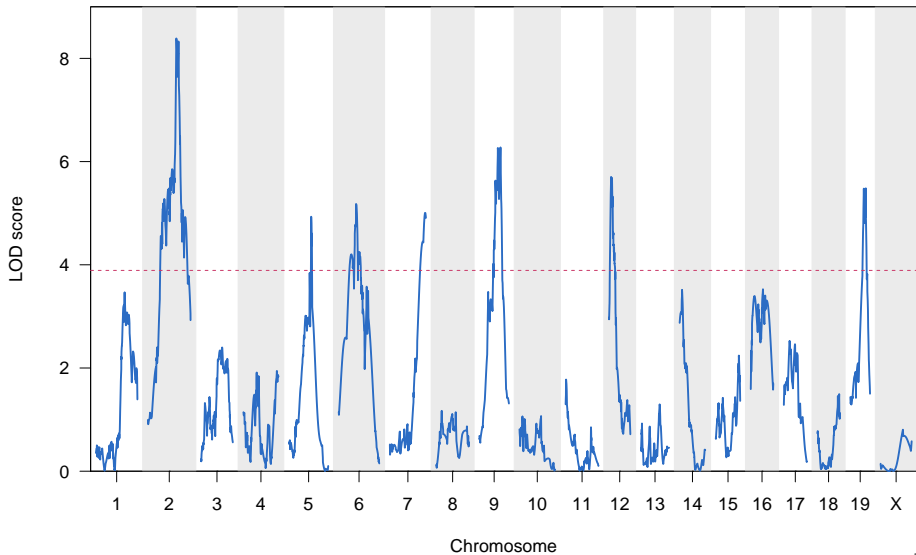
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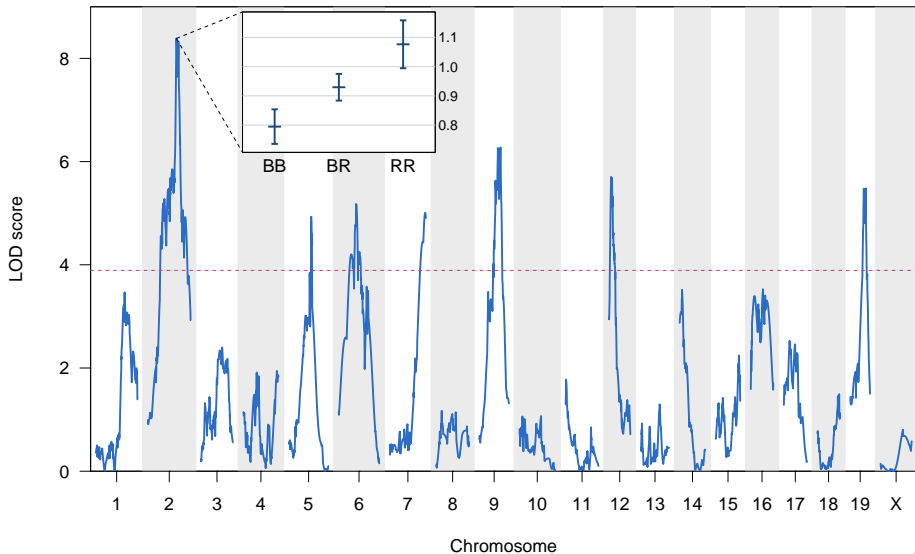
Intercross



QTL mapping



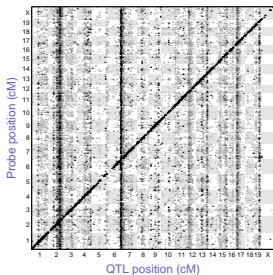
QTL mapping



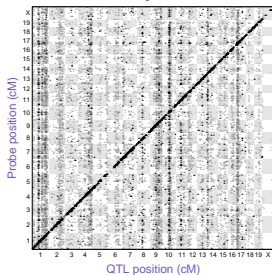


B6 × BTBR, *Lep^{ob/ob}*

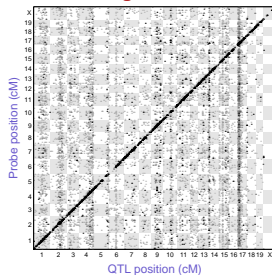
islet



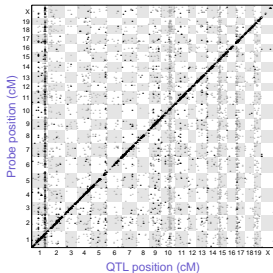
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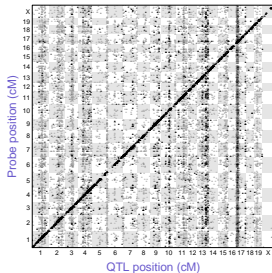
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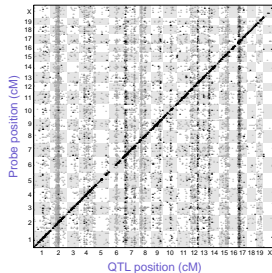
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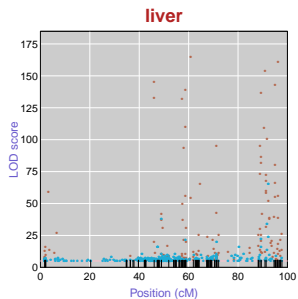
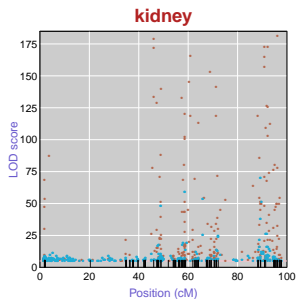
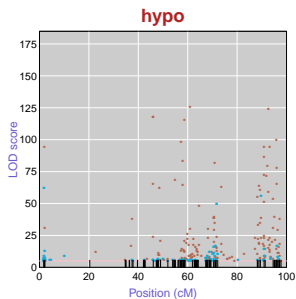
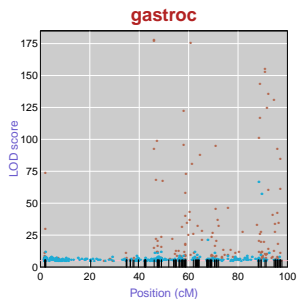
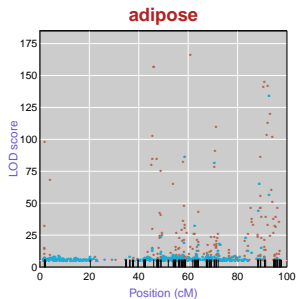
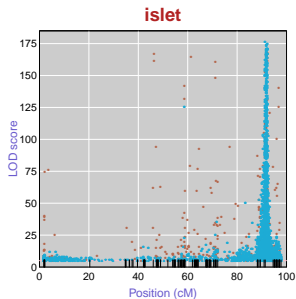
kidney



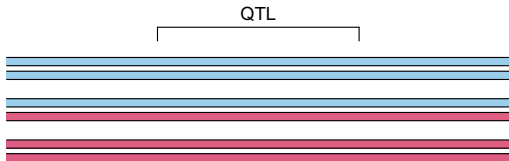
liver



Chr 6



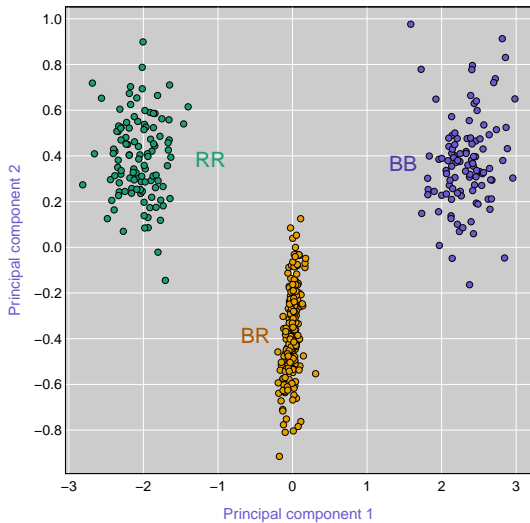
Consider the non-recombinants...



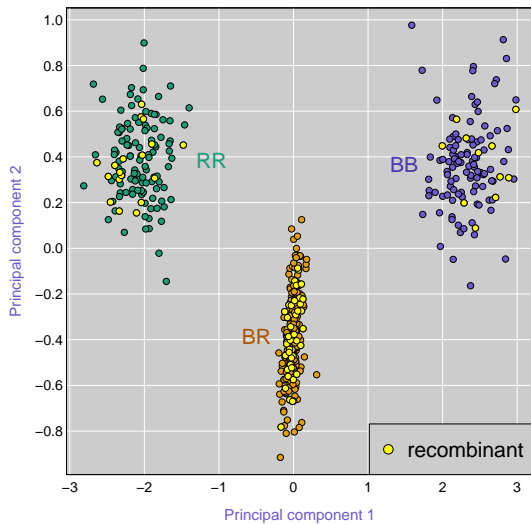
Consider the non-recombinants...



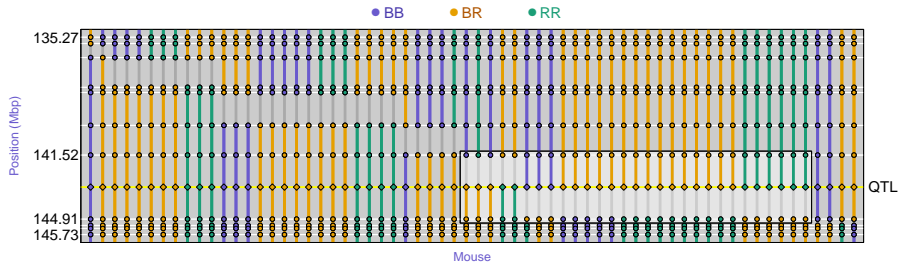
Islet c6 PCs



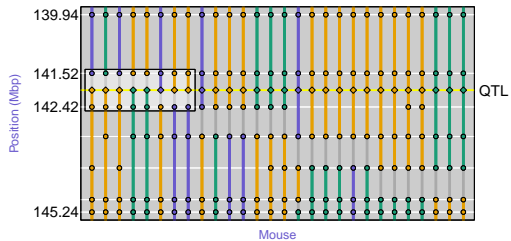
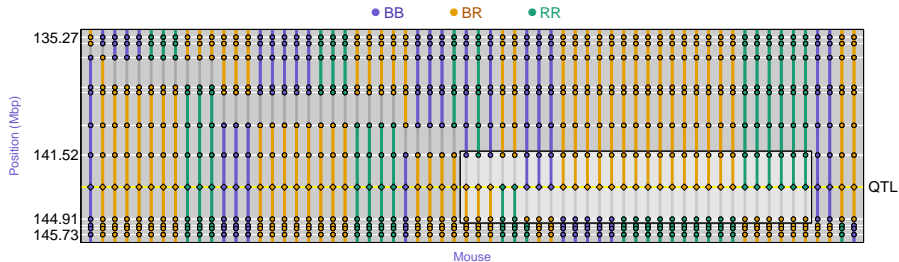
Islet c6 PCs



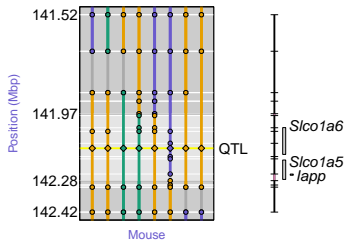
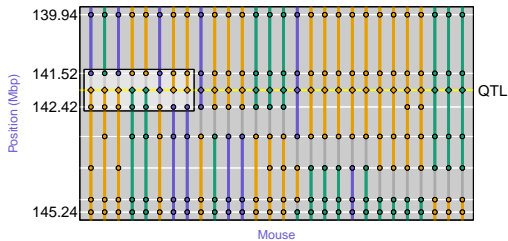
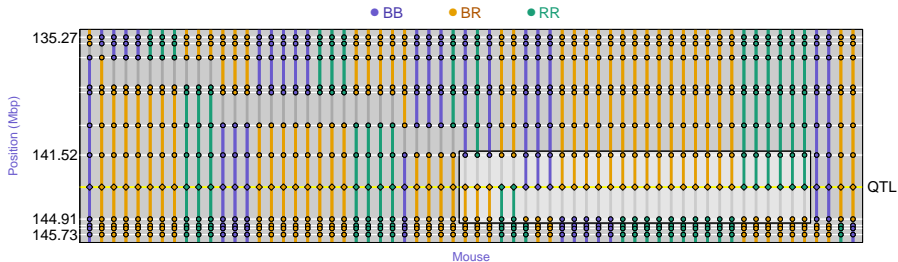
Fine-mapping the c6 locus



Fine-mapping the c6 locus

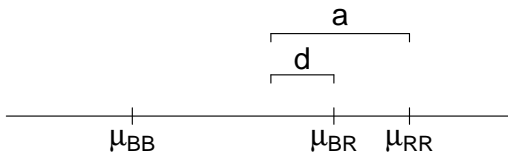


Fine-mapping the c6 locus

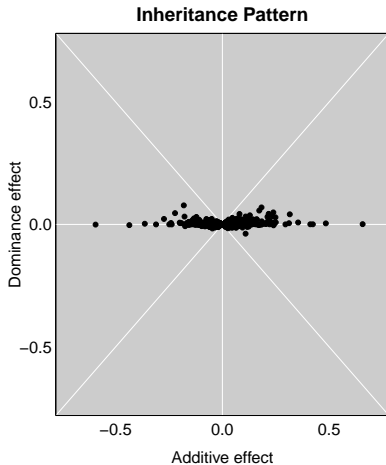
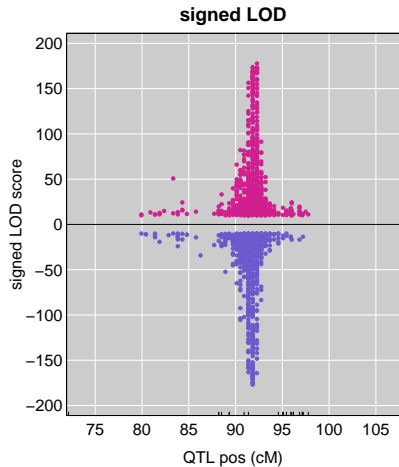


Is it one QTL?

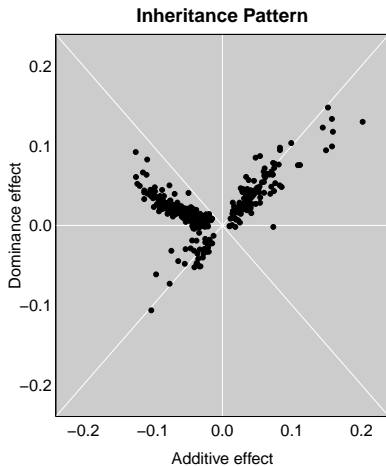
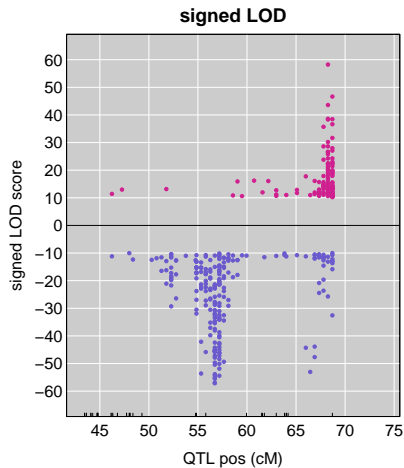
Consider the QTL effects...



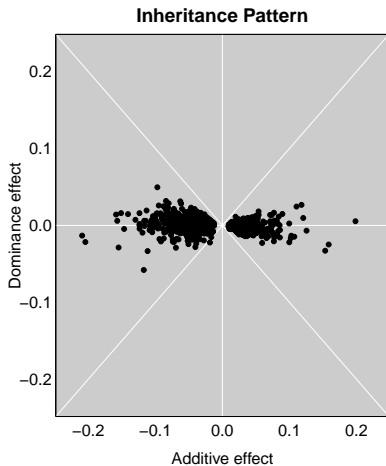
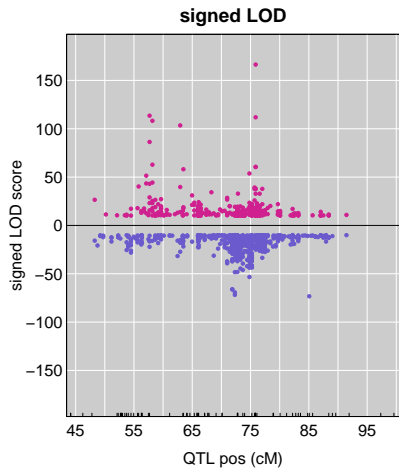
eQTL effects: Islet c6



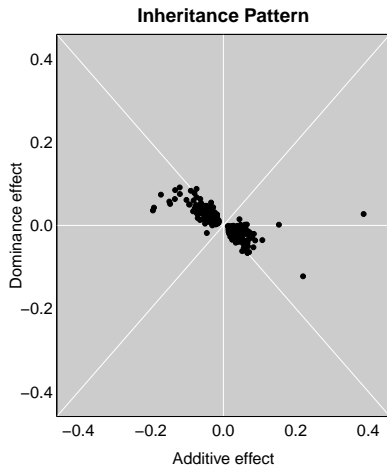
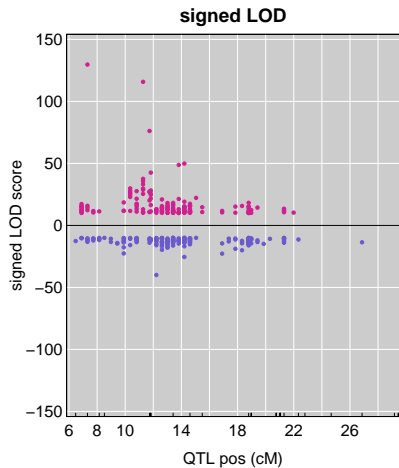
eQTL effects: Kidney c13



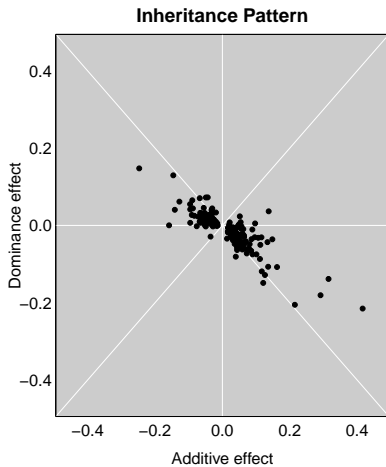
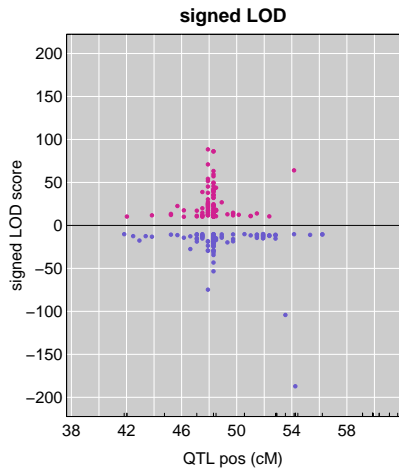
eQTL effects: Islet c2



eQTL effects: Liver c17

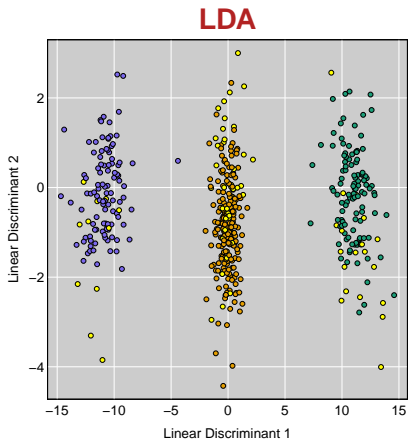


eQTL effects: Adipose c10



Compare the recombinants
and non-recombinants.

LDA & PCA: Islet c6

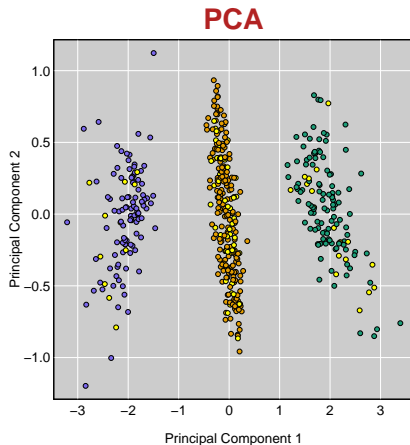


● BB

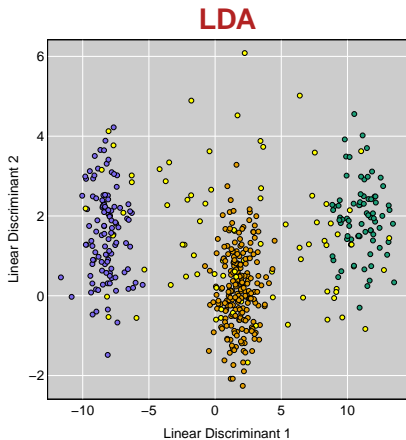
● BR

● RR

● Recombinant



LDA & PCA: Islet c2

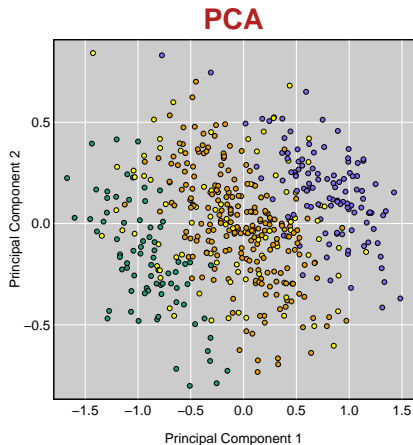


● BB

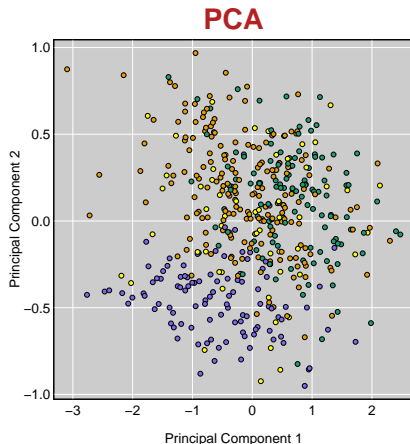
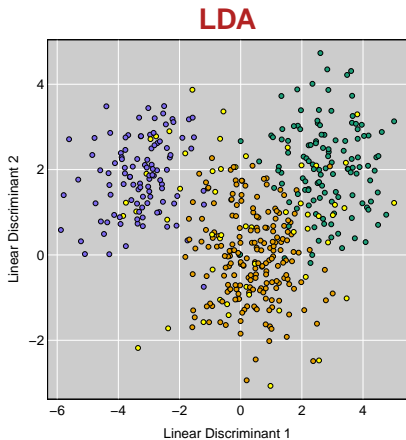
● BR

● RR

● Recombinant



LDA & PCA: Kidney c13



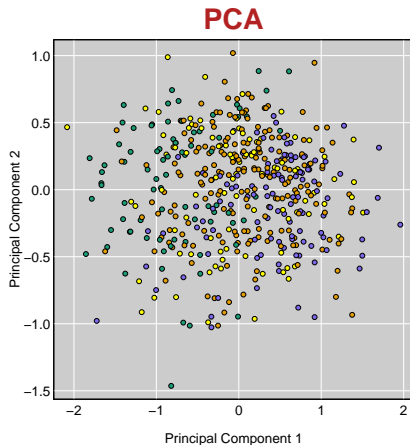
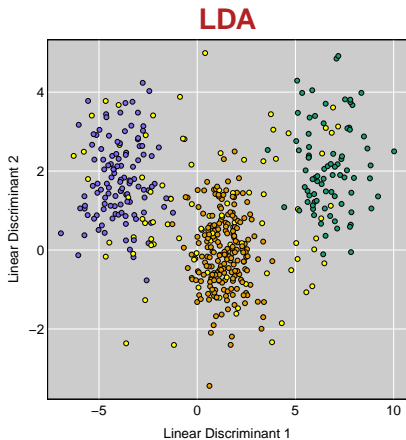
● BB

● BR

● RR

● Recombinant

LDA & PCA: Liver c17



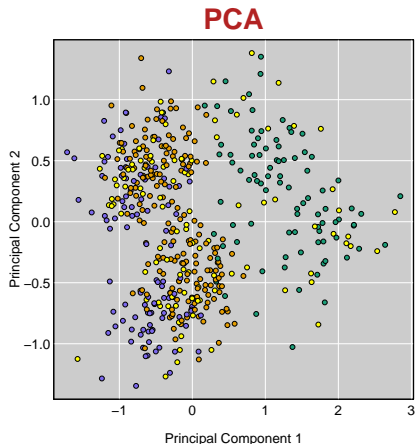
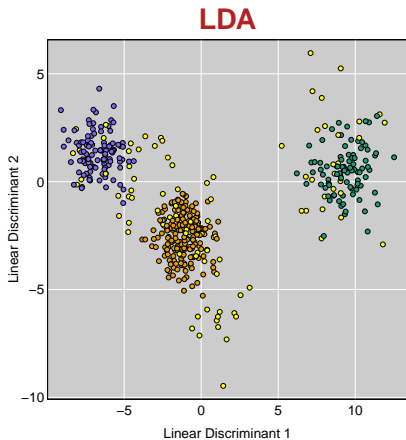
● BB

● BR

● RR

● Recombinant

LDA & PCA: Adipose c10



● BB

● BR

● RR

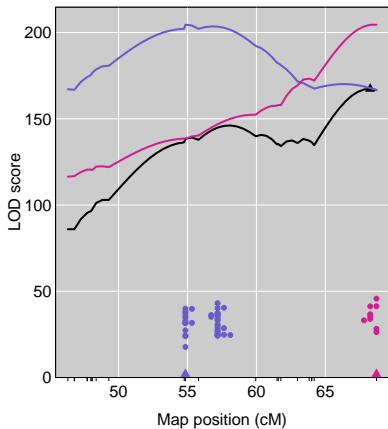
● Recombinant

Formal test for 1 vs 2 QTL

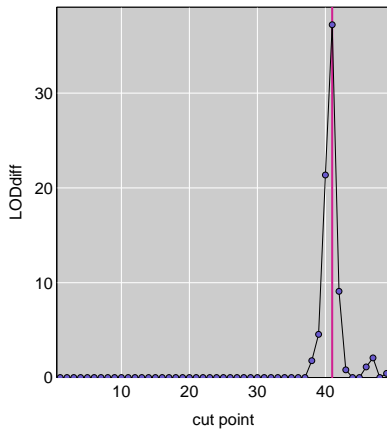
- ▶ Consider a set of traits mapping to common eQTL
- ▶ Multivariate QTL analysis with 1 or 2 QTL
- ▶ With 2-QTL model, each trait affected by one or the other QTL
 - Order traits by estimated QTL location when considered separately
 - Consider cut points of the list, assign first group to one QTL and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

1 vs 2 QTL: Kidney c13

LOD profile

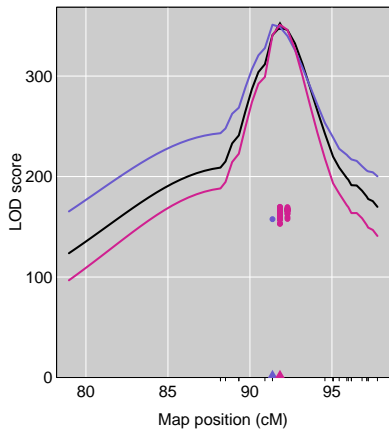


LOD diff by cutpoint

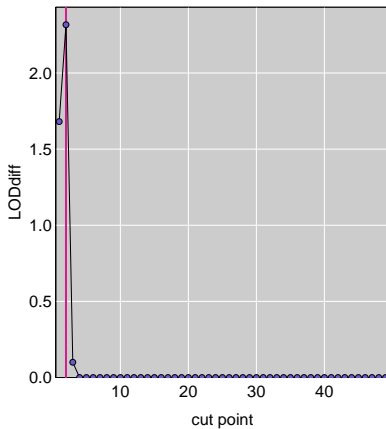


1 vs 2 QTL: Islet c6

LOD profile

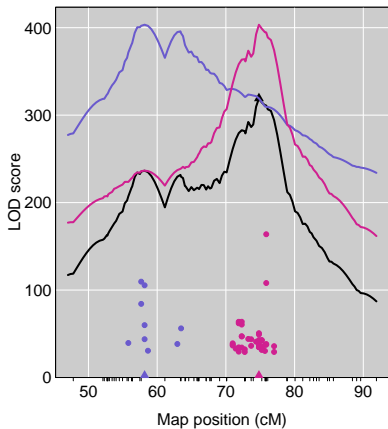


LOD diff by cutpoint

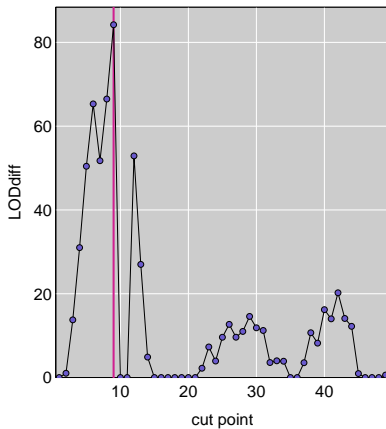


1 vs 2 QTL: Islet c2

LOD profile

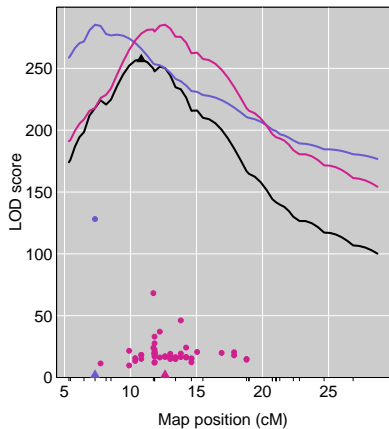


LOD diff by cutpoint

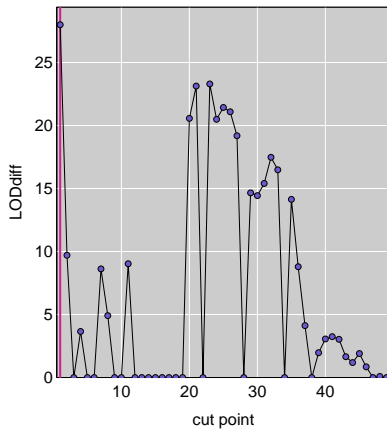


1 vs 2 QTL: Liver c17

LOD profile

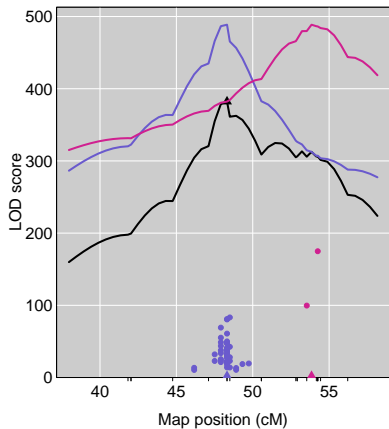


LOD diff by cutpoint

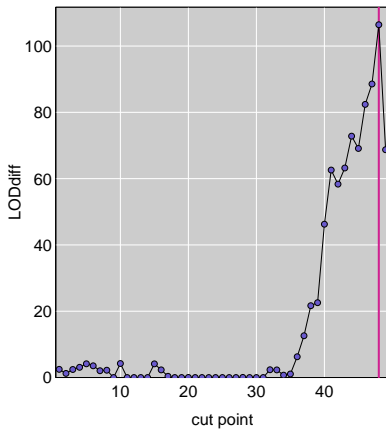


1 vs 2 QTL: Adipose c10

LOD profile



LOD diff by cutpoint



Summary

- ▶ Fine-mapping a *trans*-eQTL hotspot
 - Consider the non-recombinants
 - Predict QTL genotype of recombinants
→ Mendelian trait
 - Fine-map by traditional means

- ▶ Large-effect locus on chr 6
 - Affects expression of ~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

Acknowledgments

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Mt. Sinai

Eric Schadt

NIH: R01 GM074244, R01 DK066369

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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

Tian J et al. (2016) The dissection of expression quantitative trait locus hotspots. *Genetics* 202:1563–1574