

Dissecting and fine-mapping *trans*-eQTL hotspots

Karl Broman & Jianan Tian

Biostatistics & Medical Informatics, UW–Madison

kbroman.org

github.com/kbroman

@kbroman

Slides: bit.ly/CTC2015

github.com/jianan



Short Course on Systems Genetics

- ▶ Jackson Lab, Bar Harbor, Maine, 27 Sep – 3 Oct, 2015
- ▶ bit.ly/JaxSysGen2015
- ▶ QTL + gene expression + network analysis → systems
- ▶ 2014 instructors included:

Gary Churchill

Karl Broman

Śaunak Sen

Rafael Irizarry

Elias Chaibub Neto

Greg Carter

Elissa Chesler

Eleanor Feingold

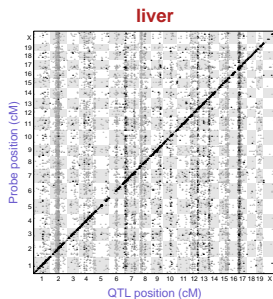
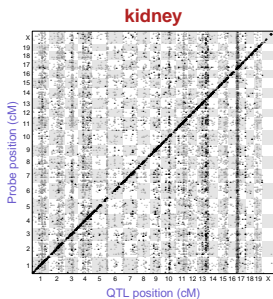
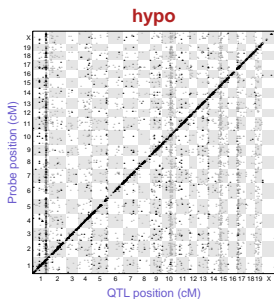
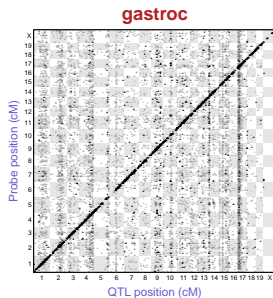
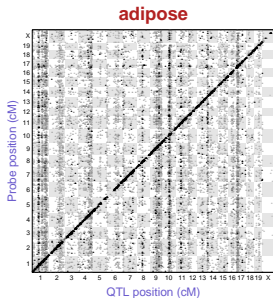
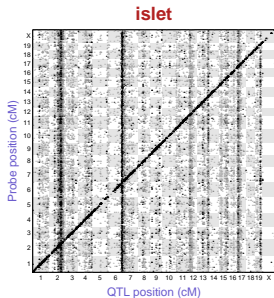
Alan Attie

Steve Horvath

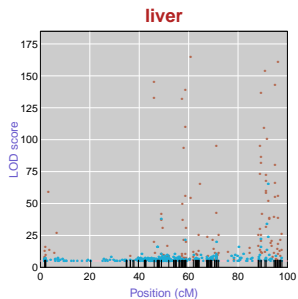
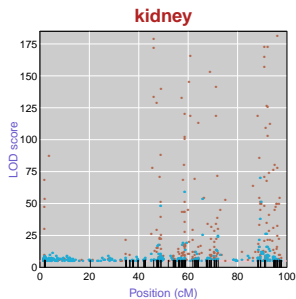
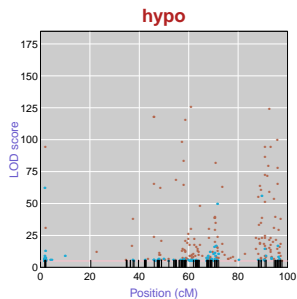
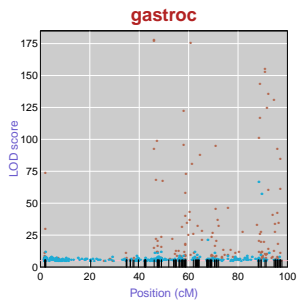
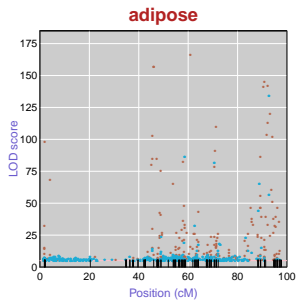
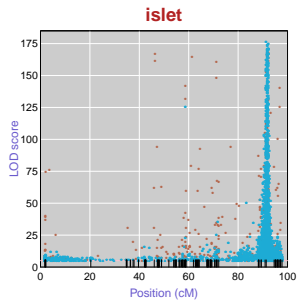
Christina Kendziorski

Shawn Gomez

B6 \times BTBR, *Lep^{ob/ob}*

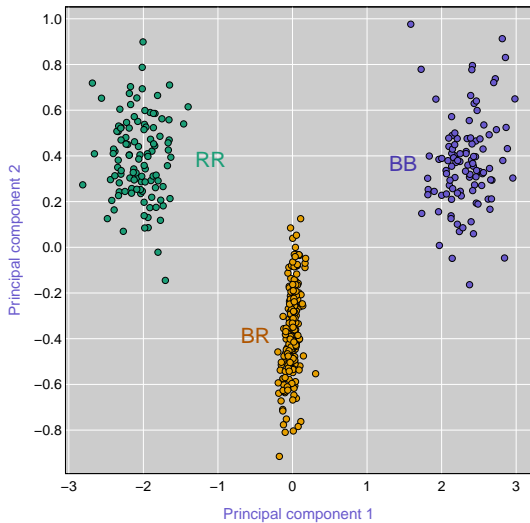


Chr 6

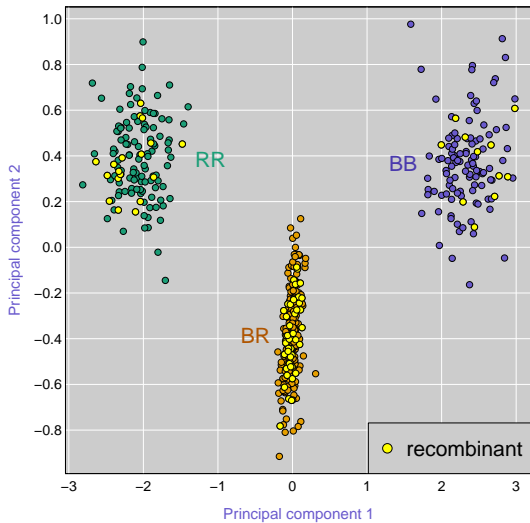


Consider the non-recombinants...

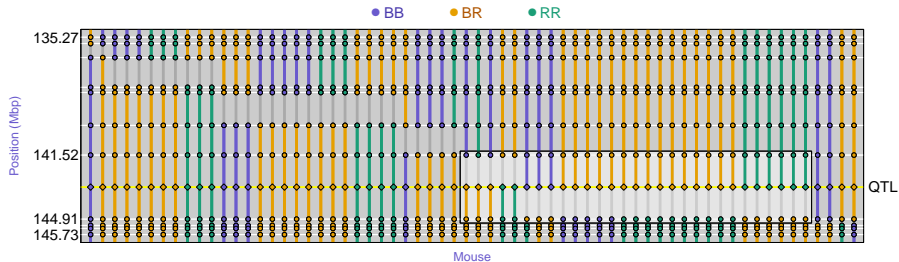
Islet c6 PCs



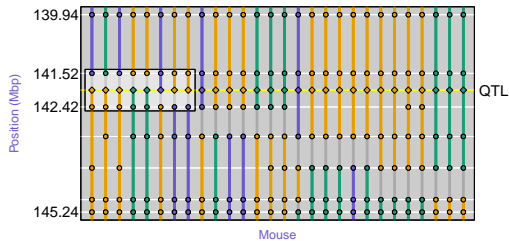
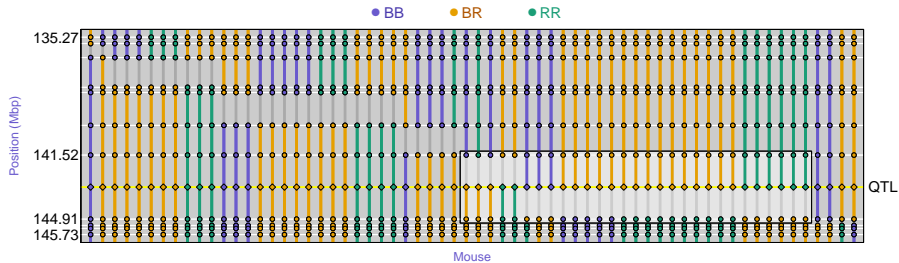
Islet c6 PCs



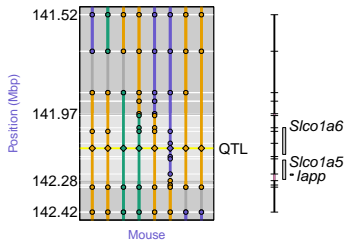
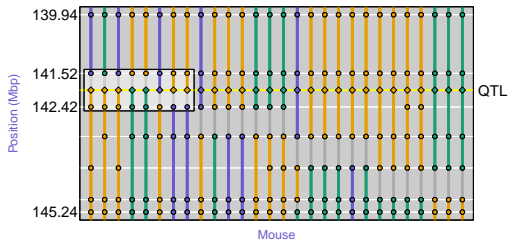
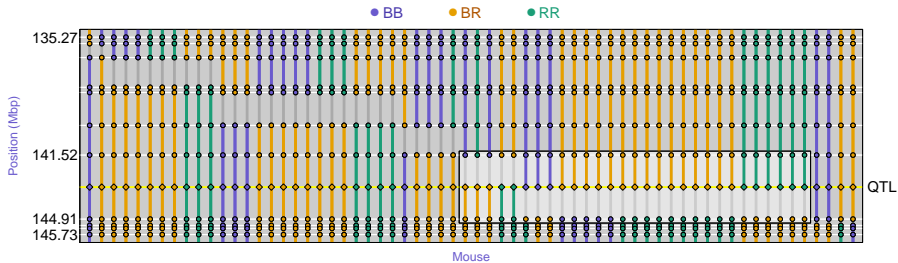
Fine-mapping the c6 locus



Fine-mapping the c6 locus



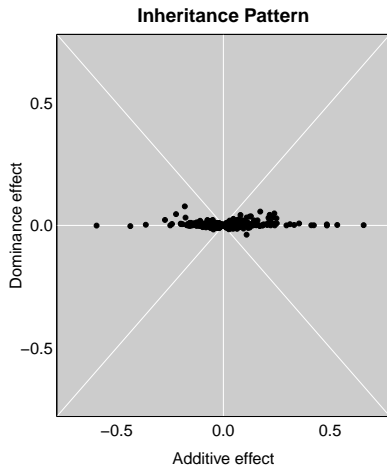
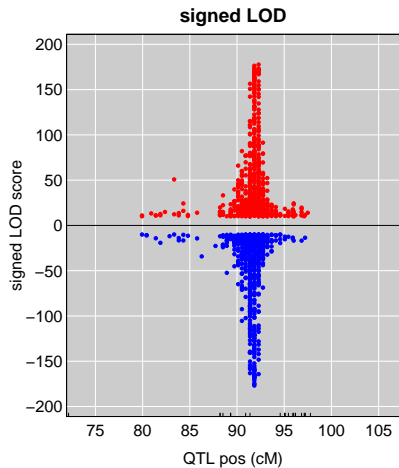
Fine-mapping the c6 locus



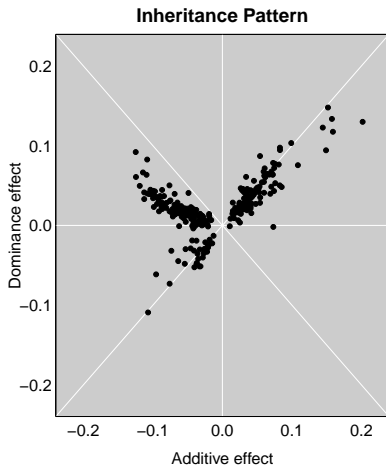
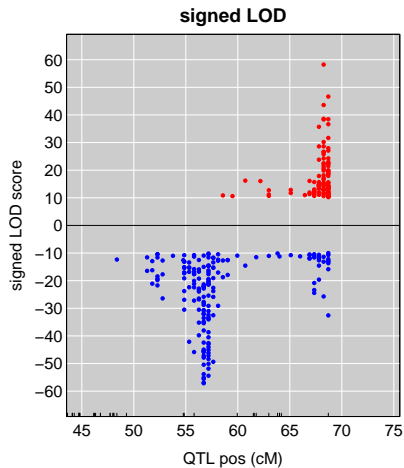
Is it one QTL?

Consider the QTL effects...

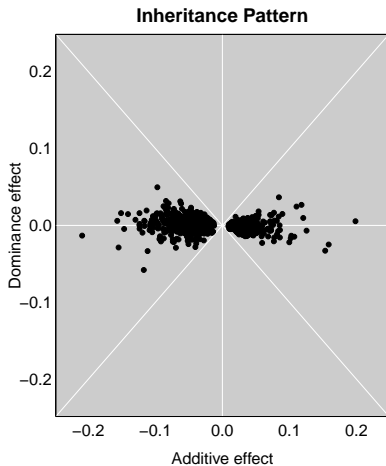
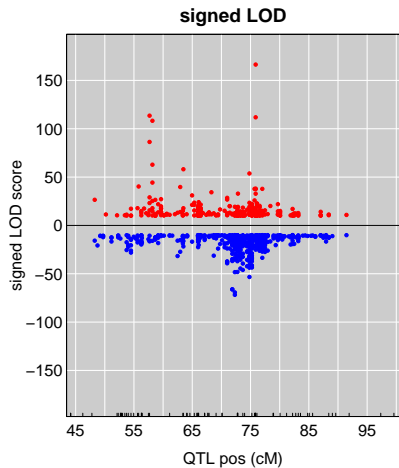
eQTL effects: Islet c6



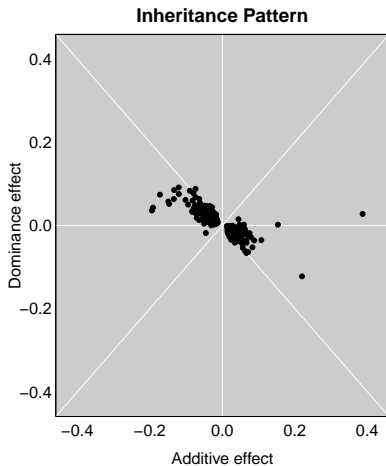
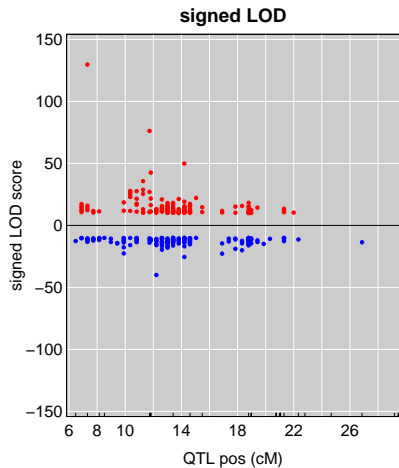
eQTL effects: Kidney c13



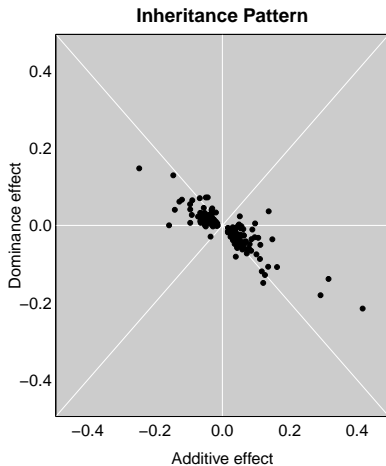
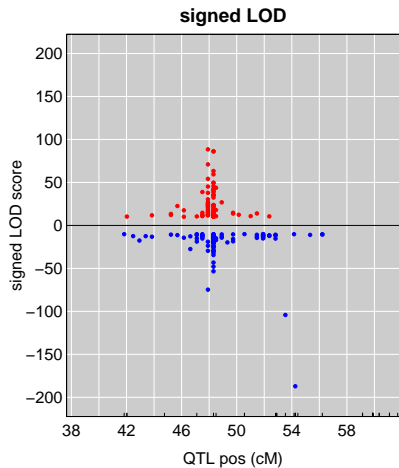
eQTL effects: Islet c2



eQTL effects: Liver c17

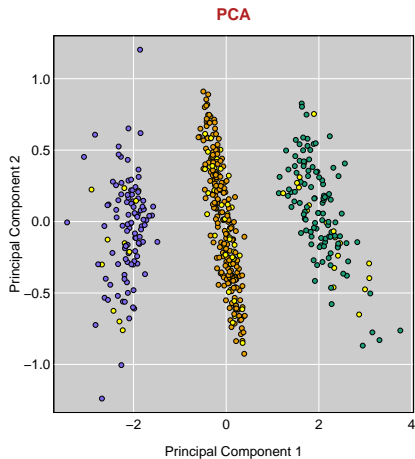
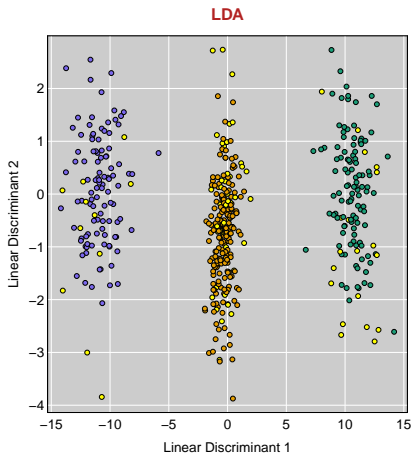


eQTL effects: Adipose c10

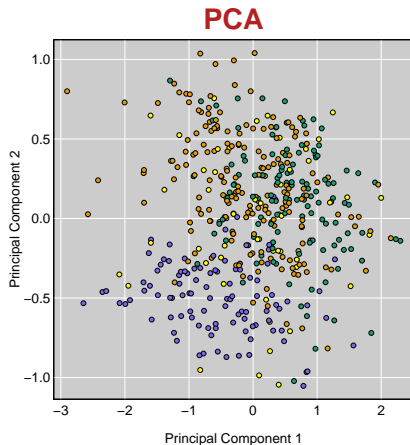
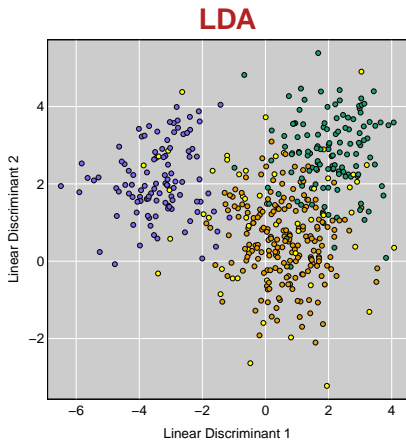


Compare the recombinants
and non-recombinants.

LDA & PCA: Islet c6



LDA & PCA: Kidney c13



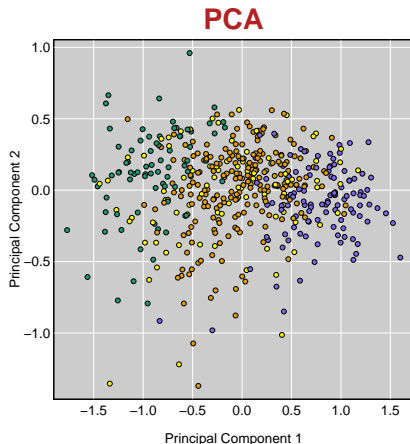
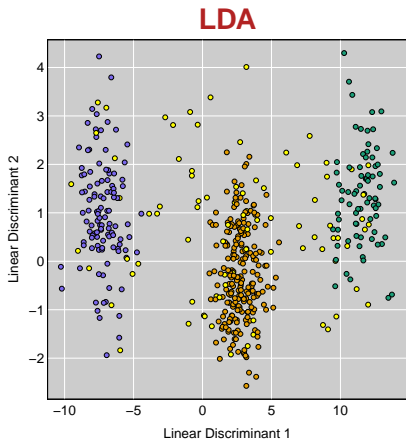
● BB

● BR

● RR

● Recombinant

LDA & PCA: Islet c2



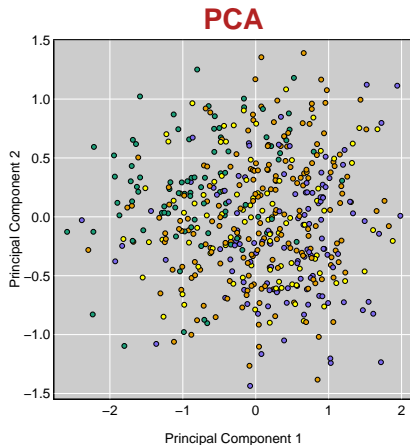
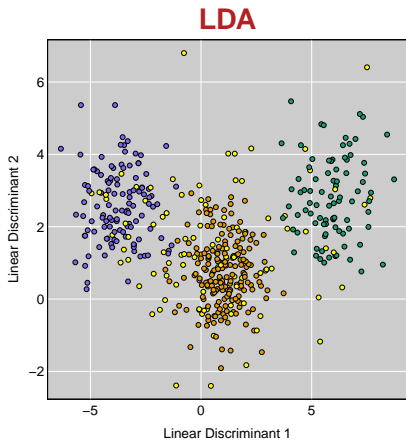
● BB

● BR

● RR

● Recombinant

LDA & PCA: Liver c17



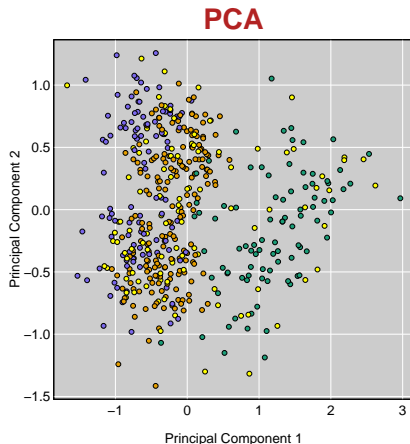
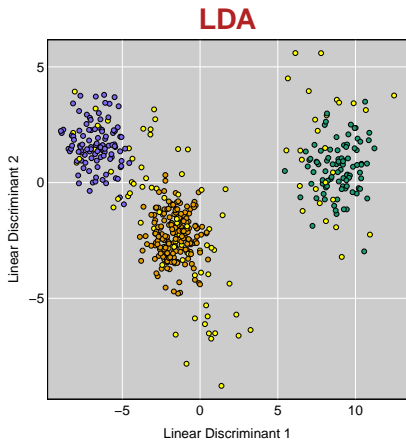
● BB

● BR

● RR

● Recombinant

LDA & PCA: Adipose c10



● BB

● BR

● RR

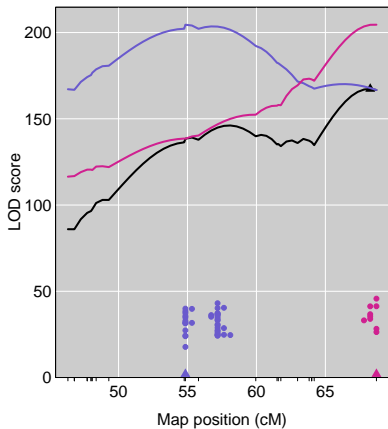
● Recombinant

Formal test for 1 vs 2 QTL

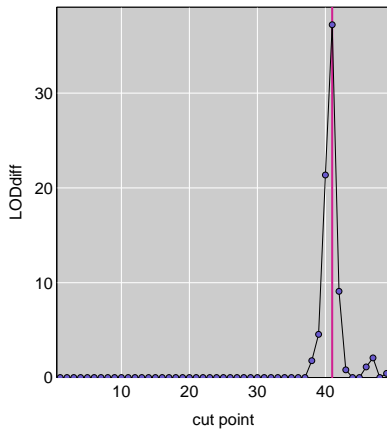
- ▶ Consider a set of traits mapping to common eQTL
- ▶ Multivariate QTL analysis with 1 or 2 QTL
- ▶ With 2-QTL model, each trait affected by one or the other QTL
 - Order traits by estimated QTL location when considered separately
 - Consider cut points of the list, assign first group to one QTL and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

1 vs 2 QTL: Kidney c13

LOD profile

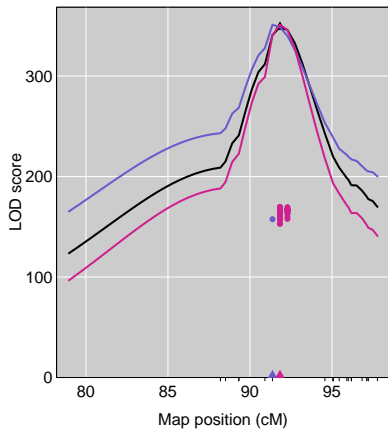


LOD diff by cutpoint

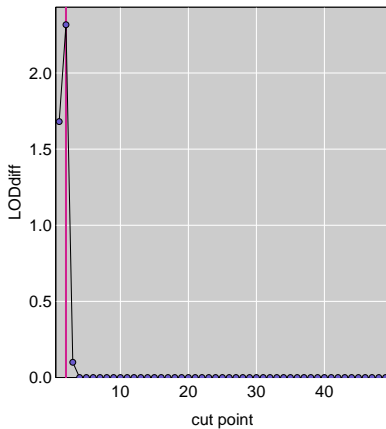


1 vs 2 QTL: Islet c6

LOD profile

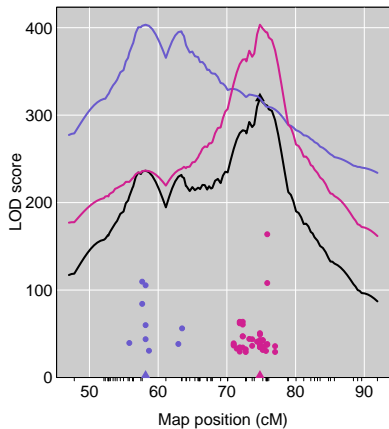


LOD diff by cutpoint

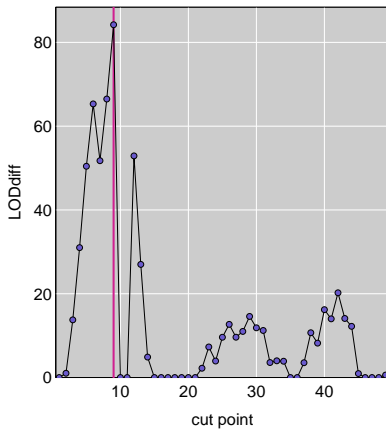


1 vs 2 QTL: Islet c2

LOD profile

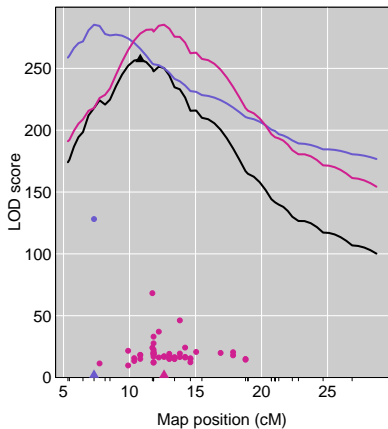


LOD diff by cutpoint

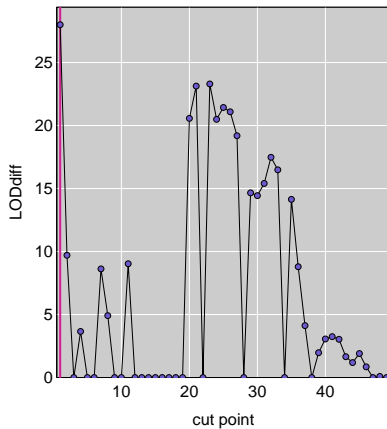


1 vs 2 QTL: Liver c17

LOD profile

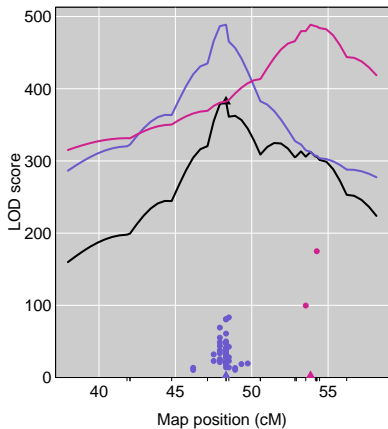


LOD diff by cutpoint

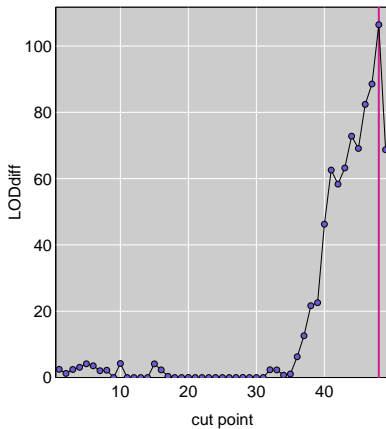


1 vs 2 QTL: Adipose c10

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

Univ. Wisconsin–Madison

Jianan Tian

Alan Attie

Mark Keller

Aimee Teo Broman

Christina Kendziorski

Brian Yandell

Angie Oler

Mary Rabaglia

Kathryn Schueler

Donald Stapleton

Univ. Kansas Medical Center

Bruno Hagenbuch

Wen Zhao

Merck & Co., Inc.

Amit Kulkarni

Mt. Sinai

Eric Schadt

NIH: R01 GM074244, R01 DK066369

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@kwbroman