Testing pleiotropy in multiparental populations

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Introduction

- 10,000+ traits with RNA sequencing and mass spectrometry

- Multiparental populations offer high-resolution QTL mapping

- New analysis tools, such as a pleiotropy test for multiparental populations, are needed

Pleiotropy & Agouti gene

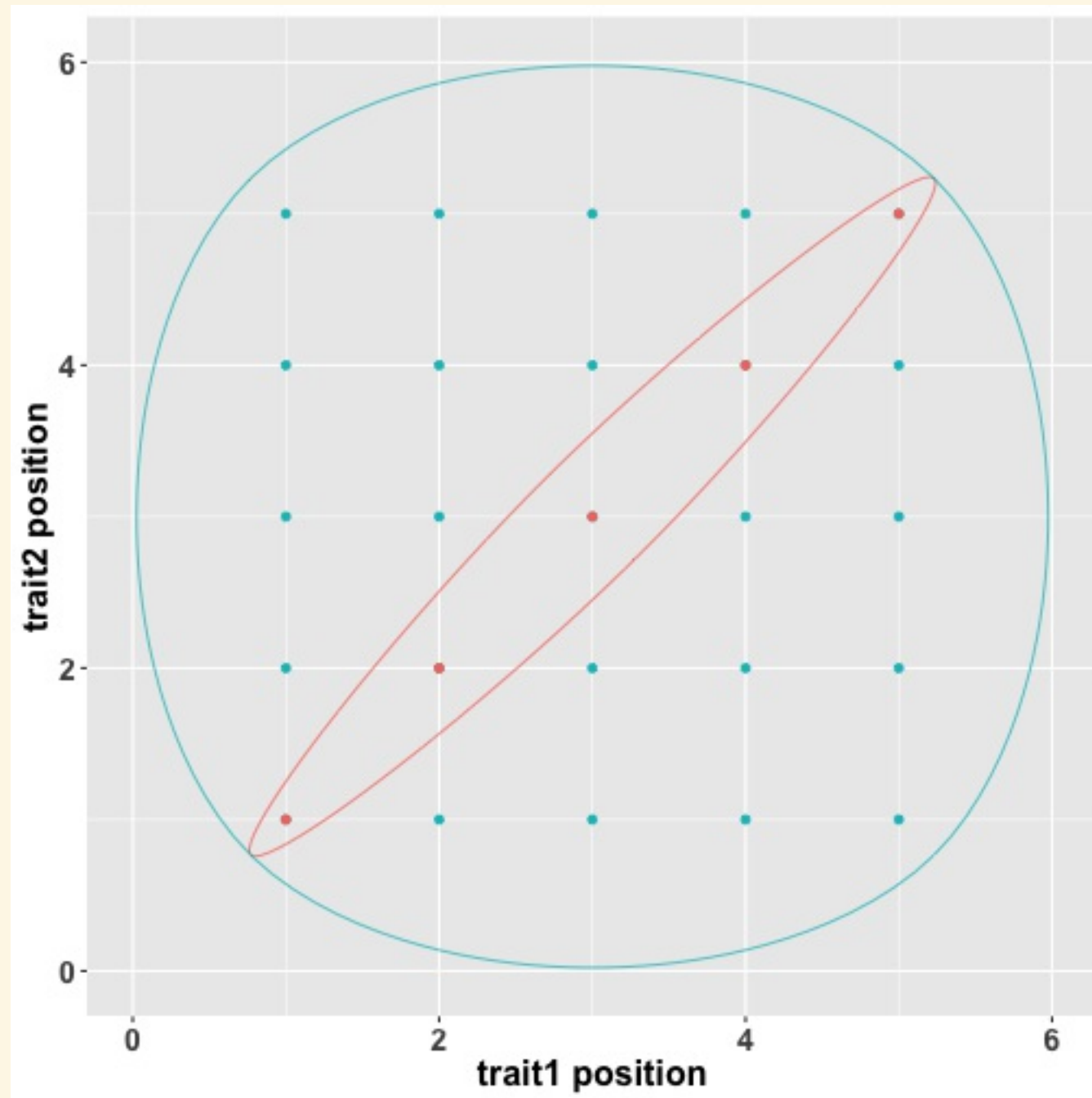https://upload.wikimedia.org/wikipedia/commons/4/4d/Agouti_Mice.jpg

Jiang and Zeng (1995) test

- Two-parent crosses

- Applies to two traits that co-map

- H_0 : Pleiotropy

- H_A : Two separate QTL

Jiang and Zeng (1995) test

- Perform a two-dimensional QTL scan

- $\text{vec}(Y) = X\text{vec}(B) + \text{vec}(E)$

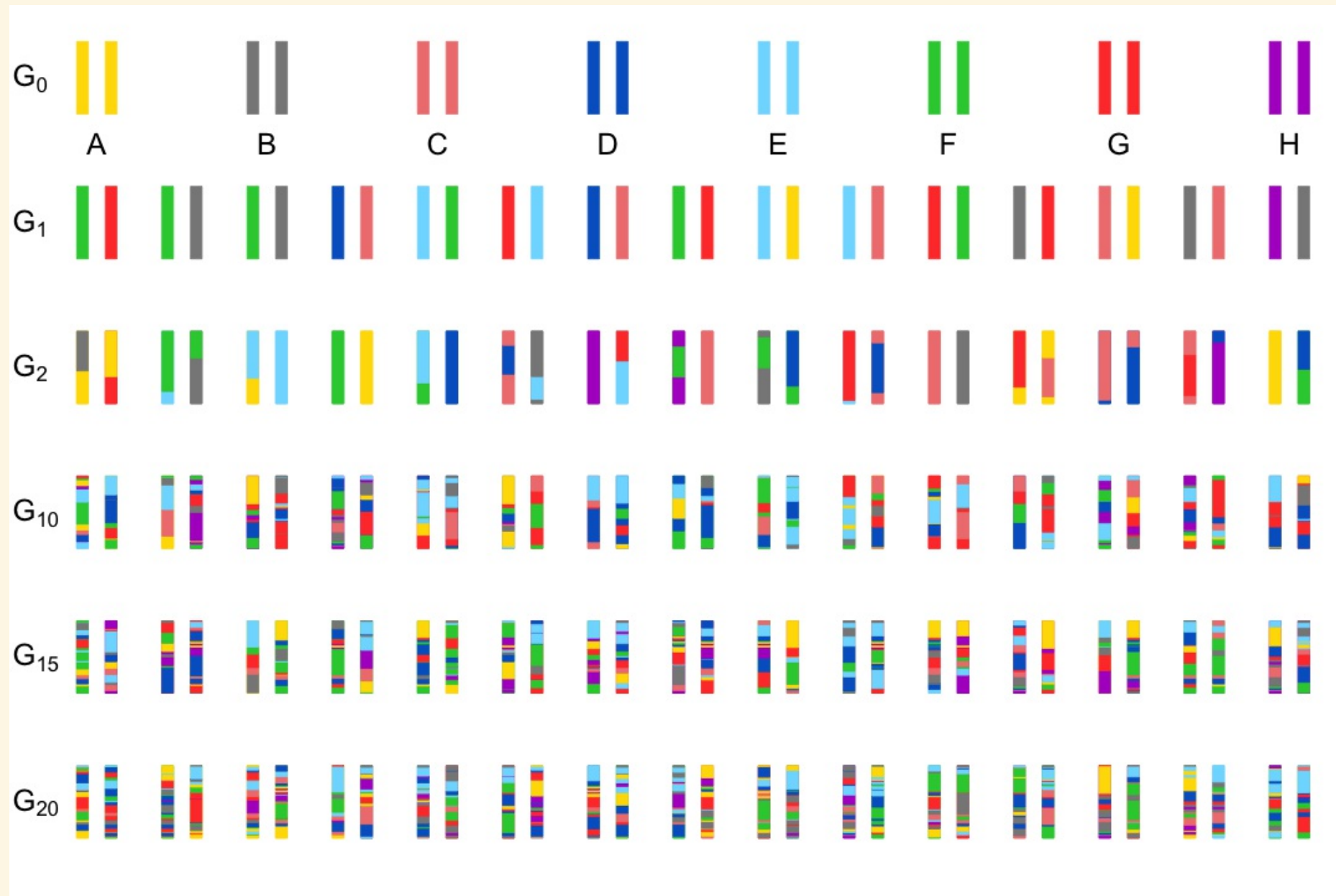- Calculate likelihood ratio test statistic

Jiang and Zeng (1995) test

Diversity Outbred Mice

- Multiparental population arising from 8 inbred lines

Multiparental populations

Challenges in multiparental populations

- Complex patterns of relatedness

- Multiple founder lines

- Determining statistical significance

Challenges in multiparental populations

- Complex patterns of relatedness

- Multiple founder lines

- Determining statistical significance

Test procedure

- Model:

$$\text{vec}(Y) = X\text{vec}(B) + \text{vec}(G) + \text{vec}(E)$$

- Calculate likelihoods

Test procedure

- Test statistic:

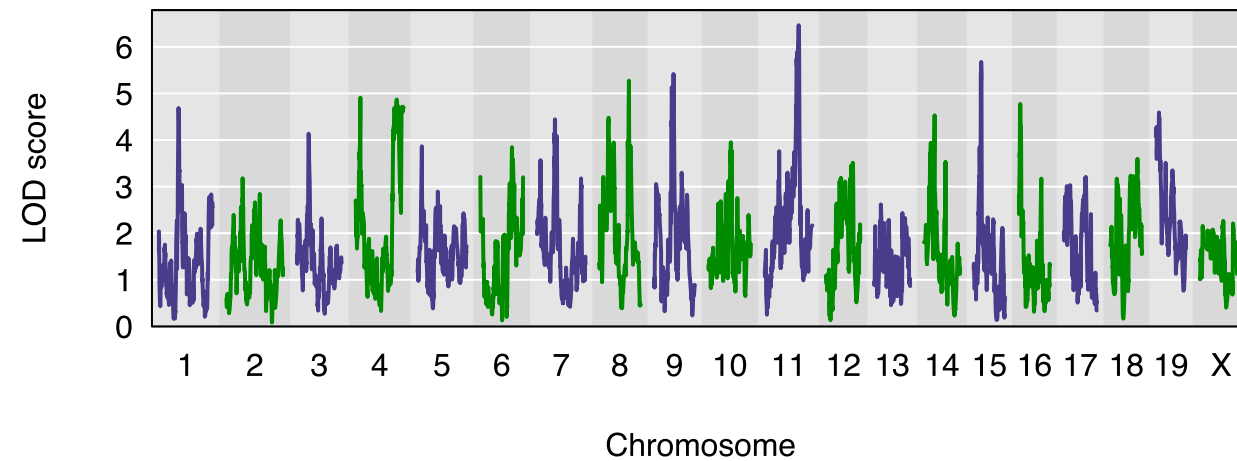$$-\log \frac{\text{max(likelihood under pleiotropy)}}{\text{max(likelihood for separate QTL)}}$$

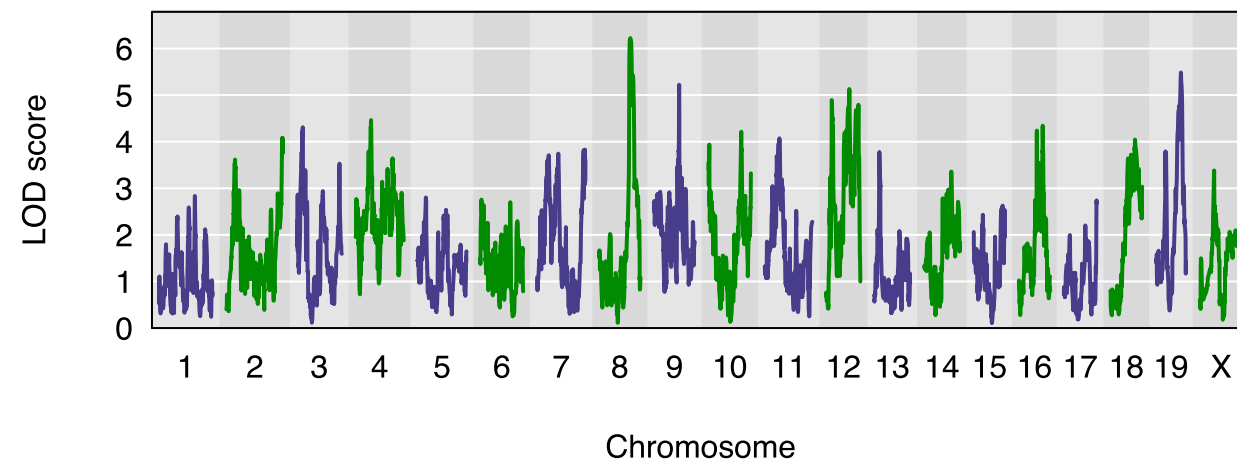- Parametric bootstrap to get p-value

Application

- Logan, et al. (2013) and Recla, et al. (2014) studied 261 Diversity Outbred mice

- Two traits map to Chr 8:

  - "hot plate latency" (57 cM)
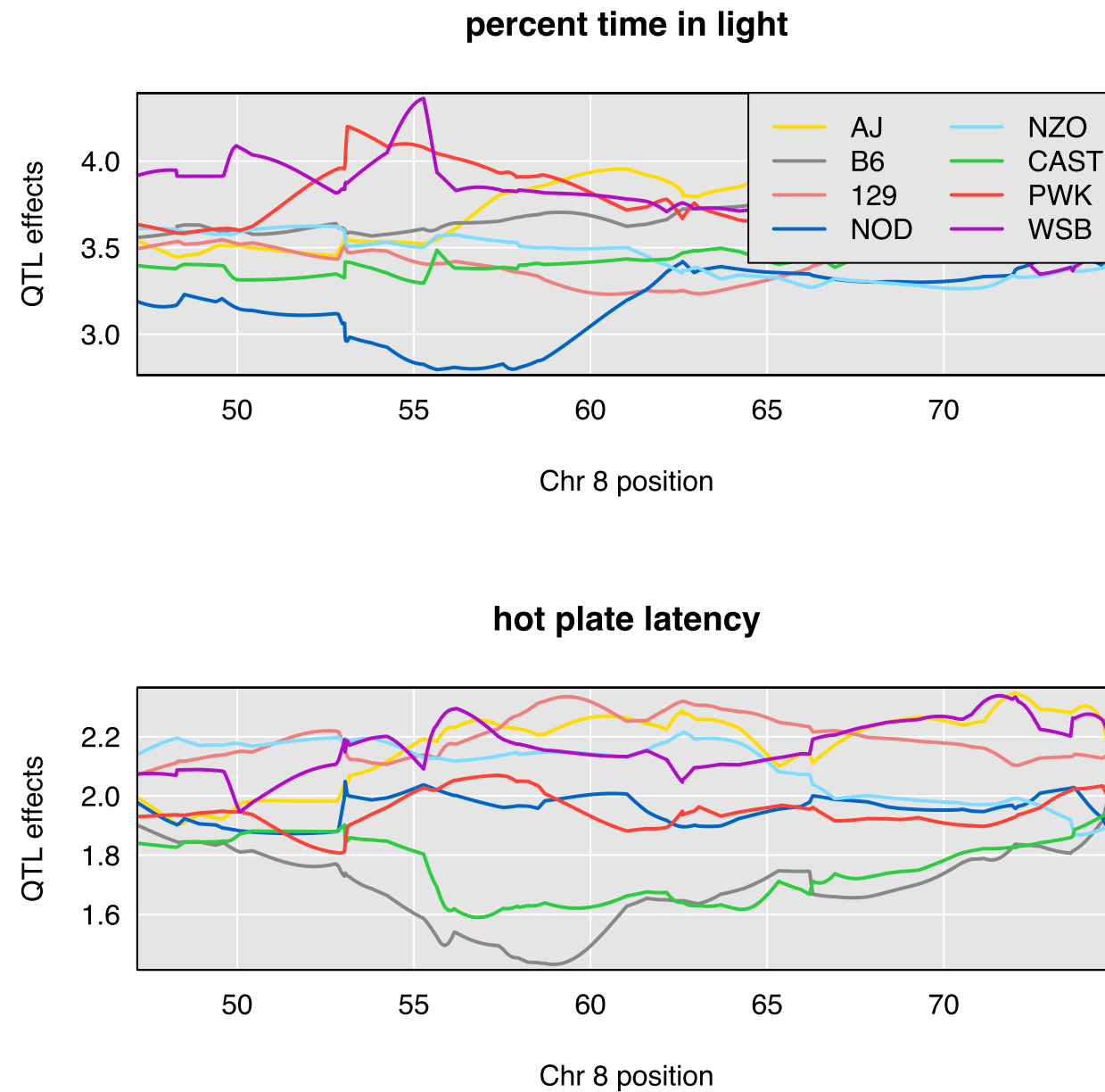
  - "percent time in light" (55 cM)

QTL scan results

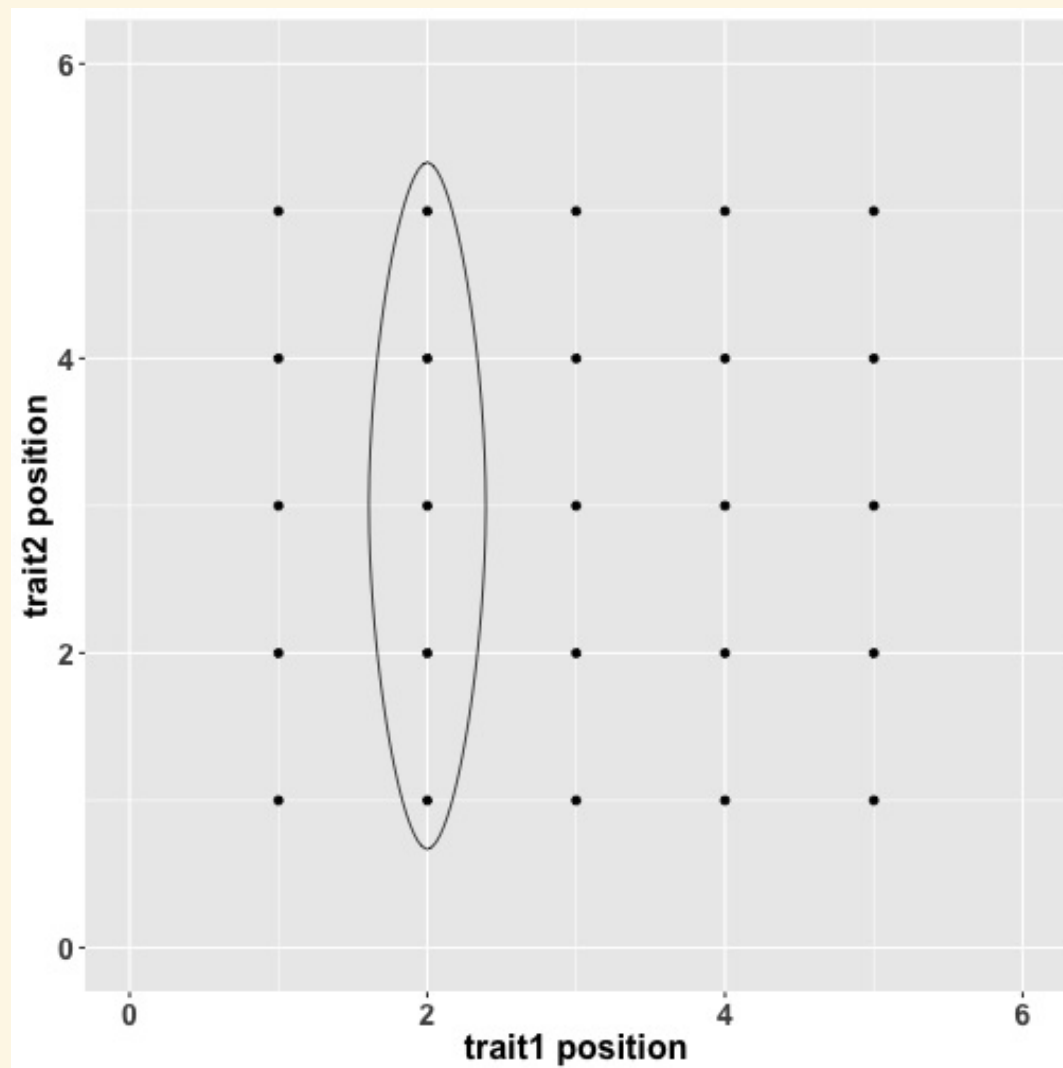**percent time in light**

hot plate latency

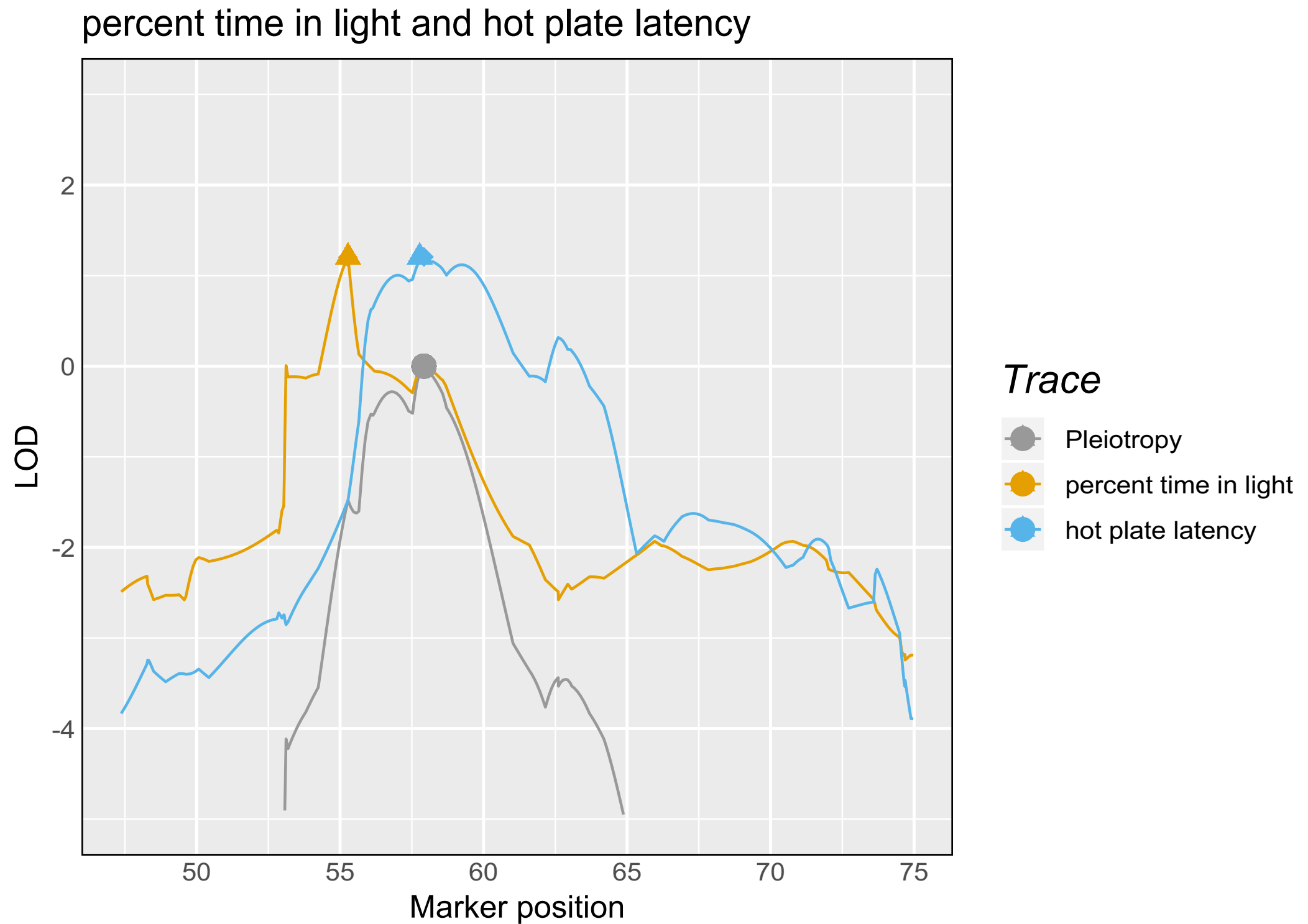# Allele effects plots

15

Profile LOD

$$\text{profile LOD}_{\text{trait 1}}(\lambda) = \max_{\lambda_2} \text{LOD}(\lambda_1, \lambda_2)$$

Profile LOD plot

Test results

- p = 0.11 (1000 bootstrap samples)

Conclusions

- Weak evidence for two separate QTL

    - One QTL affects "distance traveled in light"

    - Second QTL affects "hot plate latency"

Mediation analysis and pleiotropy testing

Mediation analysis

- Is one molecule an intermediate in a causal pathway?

Mediation analysis example

- QTL near Dhtkd1 gene affects Dhtkd1 RNA levels and DHTKD1 protein levels

- Is Dhtkd1 RNA an intermediate between QTL and DHTKD1 protein levels?

Dhtkd1_DNA ⟶ Dhtkd1_RNA ⟶ DHTKD1_Protein

Mediation analysis methods

- LOD score with and without conditioning on candidate intermediate

- LOD difference

- LOD difference proportion

Dissecting an eQTL hotspot

- Keller, et al. (2018) identified 147 nonlocal traits that map to Chr 2 (163.5 Mb to 167.5 Mb)

-             expression levels mediate 88 of 147 traits

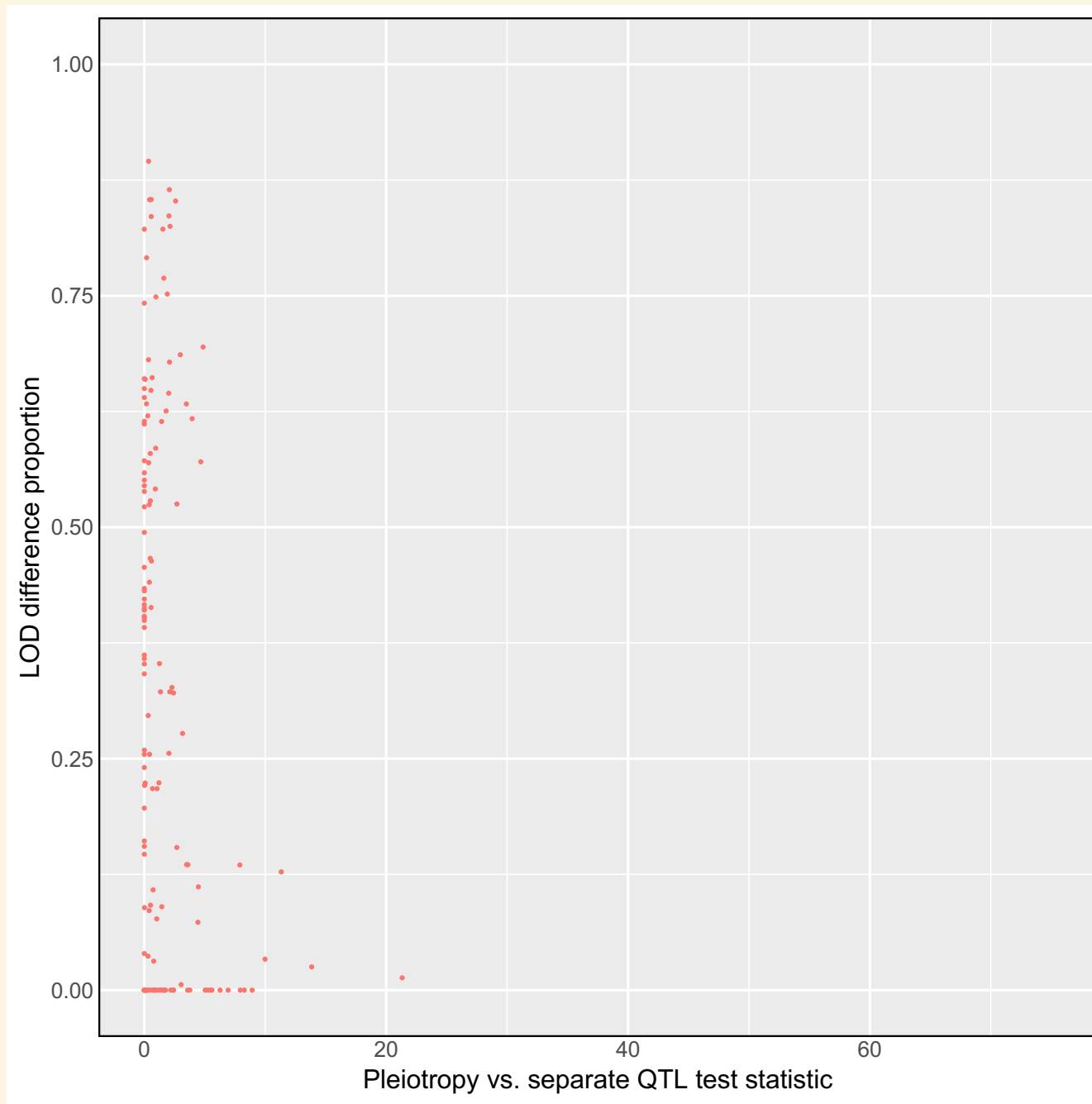- Do other local genes act as intermediates?

Dissecting an eQTL hotspot

- 13 local gene expression traits as candidate mediators

- 147 nonlocal gene expression traits

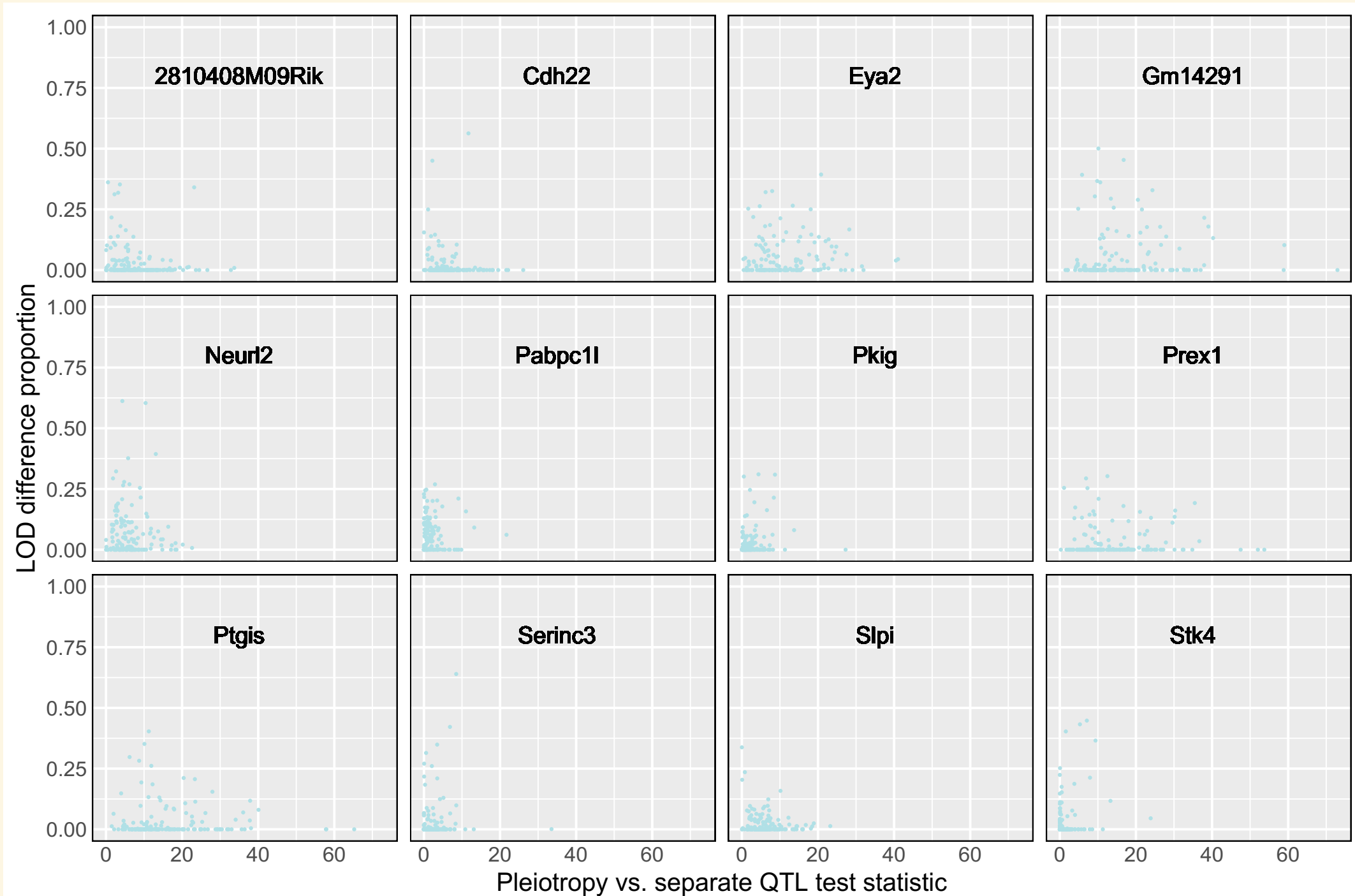- Pair one local trait with one nonlocal trait

Dissecting an eQTL hotspot
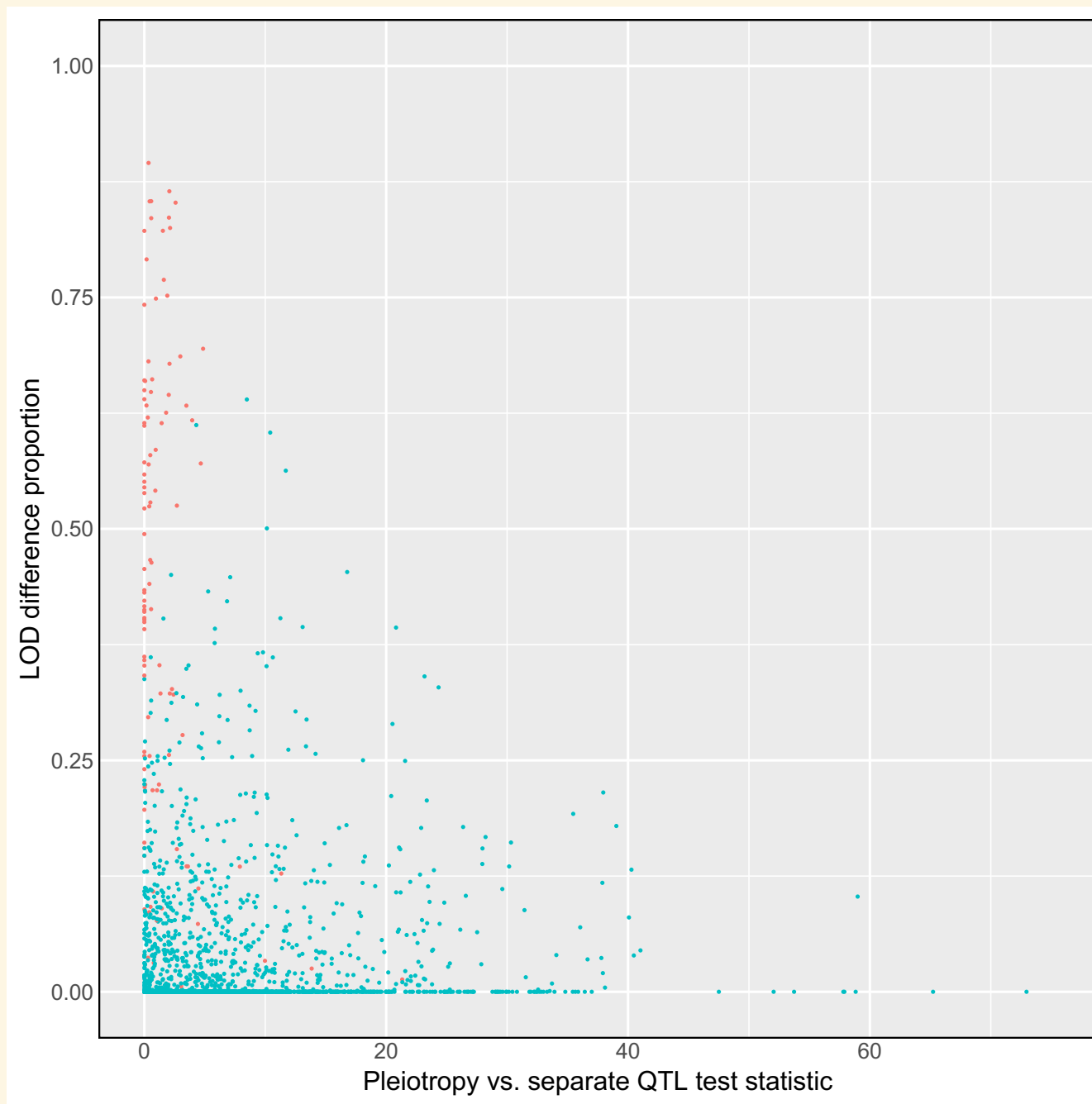
Dissecting an eQTL hotspot

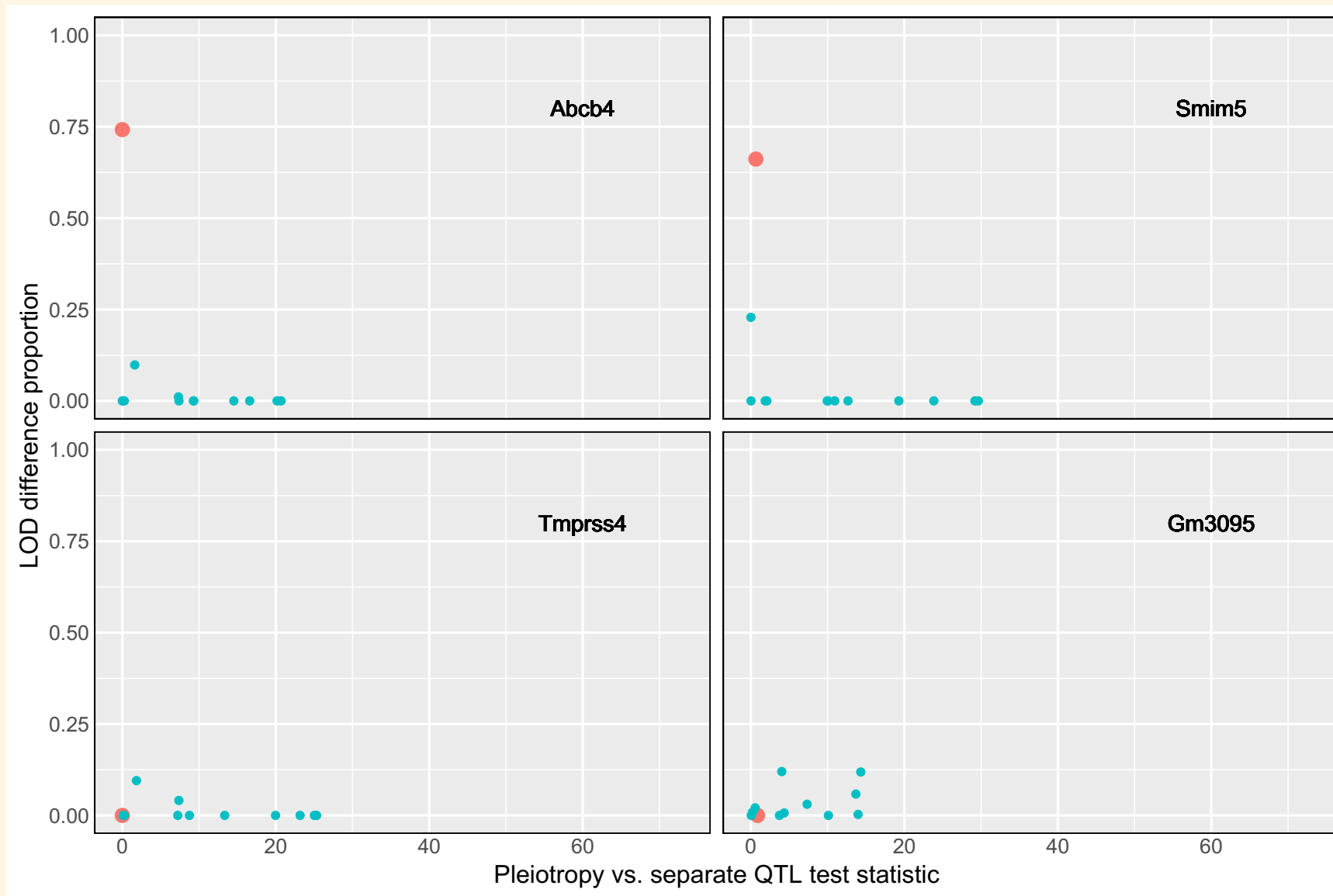# Dissecting an eQTL hotspot

Dissecting an eQTL hotspot

Conclusions

- Pleiotropy test & mediation analysis ask distinct questions

- Both are useful when dissecting eQTL hotspots

qtl2pleio R package development

Design elements

- Written mostly in R

  - Some calculations in C++, via Rcpp package

  - C++ Eigen library and RcppEigen for matrix algebra

  - User interacts only with R functions

Design elements

- Tutorial vignettes demonstrate functionality

- Unit tests included via   R package

- Documentation with   R package

- Package website with   R package

R packages book

- Hadley Wickham's "R packages" book as a guide

Open-source R package

- Hosted on github

- Install via   R package

-      commits publicly visible

- Travis CI for testing after every commit

Binder integration

- Enhances reproducibility

- Uses Docker images

- Downloads R packages for a specified date (or commit on Github)

Binder integration: 2 new files

- install.R

  - contains code to install R packages

- runtime.txt

  - contains one line of text to indicate date for CRAN packages

Contact information

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- qtl2pleio R package:
  https://github.com/fboehm/qtl2pleio

- Biorxiv pre-print: http://bit.ly/boehm-biorxiv

References

Jiang, C. and Z. Zeng (1995). "Multiple trait analysis of genetic mapping for quantitative trait loci." In: 140.3, pp. 1111-1127.

Keller, M. P, D. M. Gatti, et al. (2018). "Genetic Drivers of Pancreatic Islet Function". In: , pp. genetics-300864.

Logan, R. W, R. F. Robledo, et al. (2013). "High-precision genetic mapping of behavioral traits in the diversity outbred mouse population". In: 12.4, pp. 424-437.

References

Recla, J. M, R. F. Robledo, et al. (2014). "Precise genetic mapping and integrative bioinformatics in Diversity Outbred mice reveals Hydin as a novel pain gene". In: 25.5-6, pp. 211-222.