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
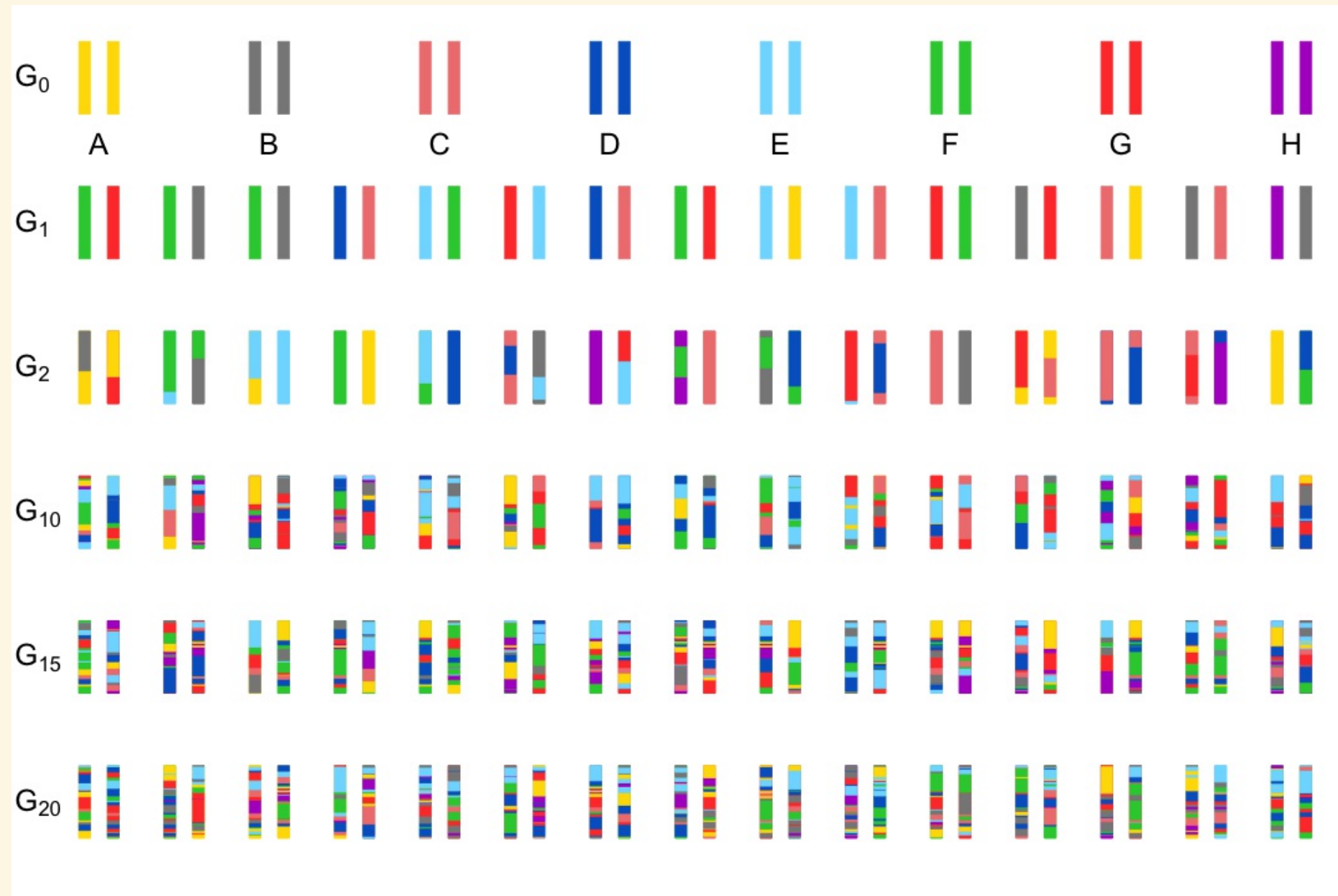
Photo by Alan Attie

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 two-QTL scan

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

  - Calculate likelihood at each ordered pair of positions

- Calculate likelihood ratio test statistic

Multiparental populations

Challenges in multiparental populations

- Complex patterns of relatedness

Multivariate random effects

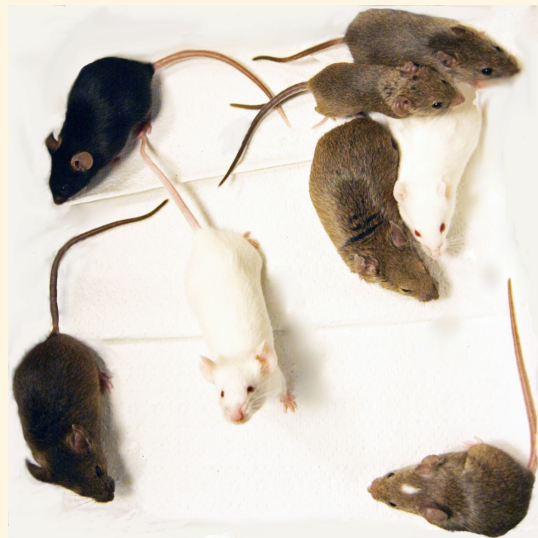- Multiple founder lines

Fixed effect for each founder allele

Photo by UNC Computational Genetics

Test procedure

- Perform a two-dimensional two-QTL scan

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

  - Calculate likelihood at each ordered pair of positions

- Calculate likelihood ratio test statistic
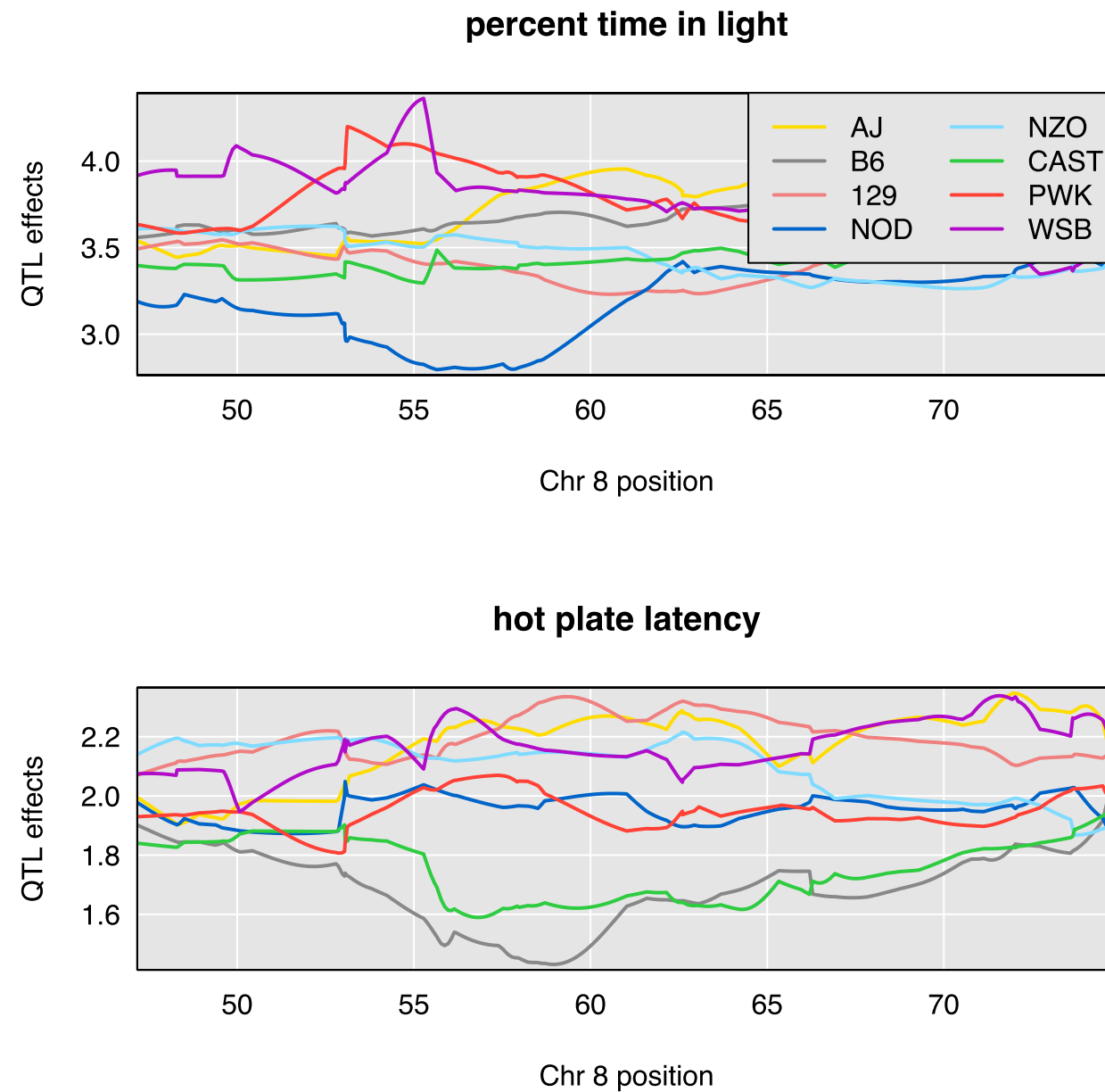
Test procedure

- Test statistic:

$$- \log_{10} \frac{\max(\text{likelihood under pleiotropy})}{\max(\text{likelihood for separate QTL})}$$

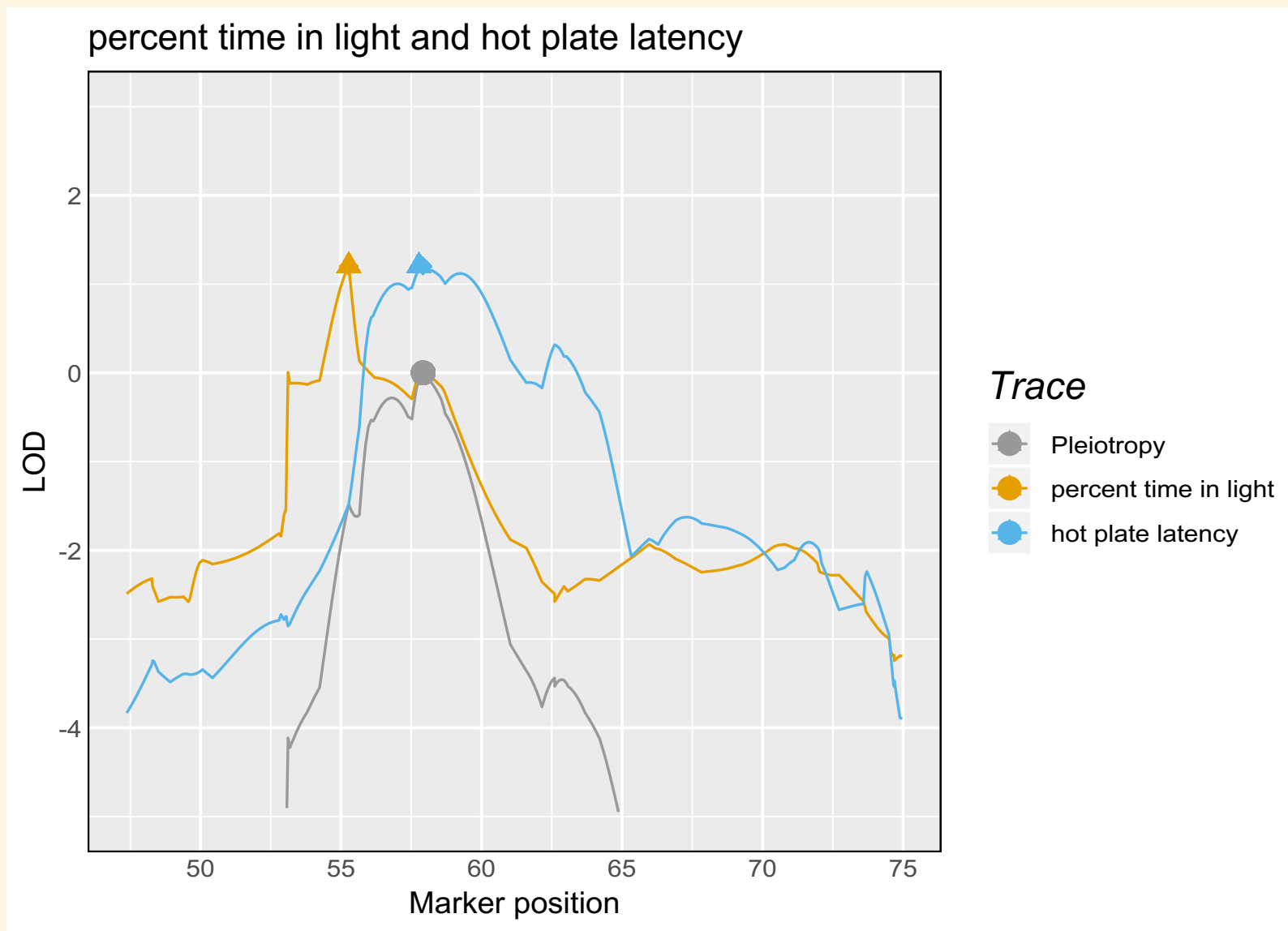- Parametric bootstrap to get a p-value

Application

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

- Measured about two dozen behavioral traits

- Two traits map to Chr 8:

  - "hot plate latency" (57 cM)

  - "percent time in light" (55 cM)

Allele effects plots

Profile LOD

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

percent time in light and hot plate latency

Test results

- $\log_{10} \Lambda = 1.2$

- $p = 0.11$ (1000 bootstrap samples)

Power study with local expression QTL

Power study: Design

- Examine power when I know true eQTL locations

  - Interlocus distance
  - Univariate LOD

- 80 local eQTL on Chr 19 (LOD > 7.2)

- 4 strong, centrally located, local eQTL chosen as "anchor" traits

  - *Asah2, Lipo1, Lipo2, 4933413C19Rik*

- Pairwise pleiotropy tests each involving one anchor and one of 79 other traits

Power study: Interlocus distance
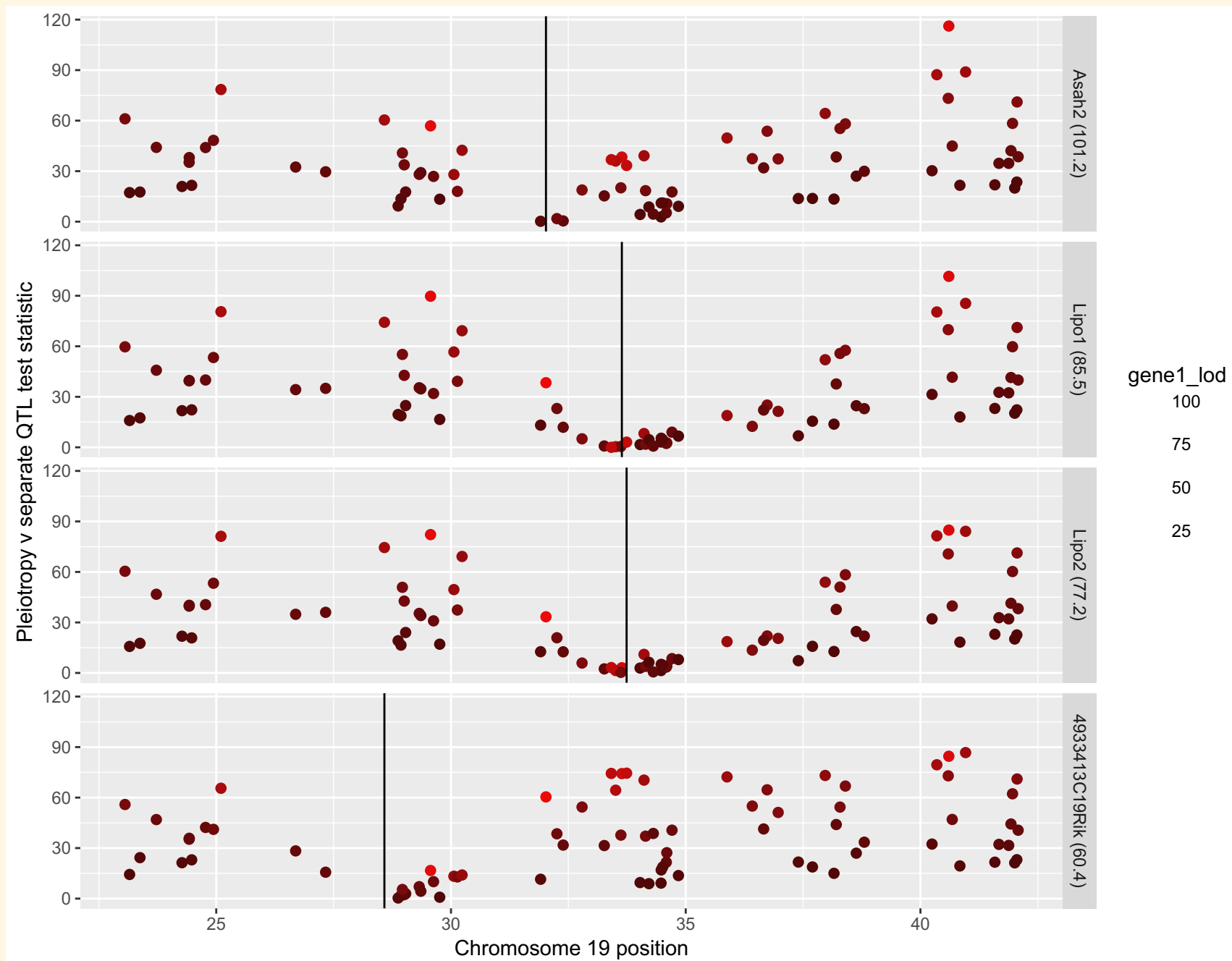
Power study: Univariate LOD
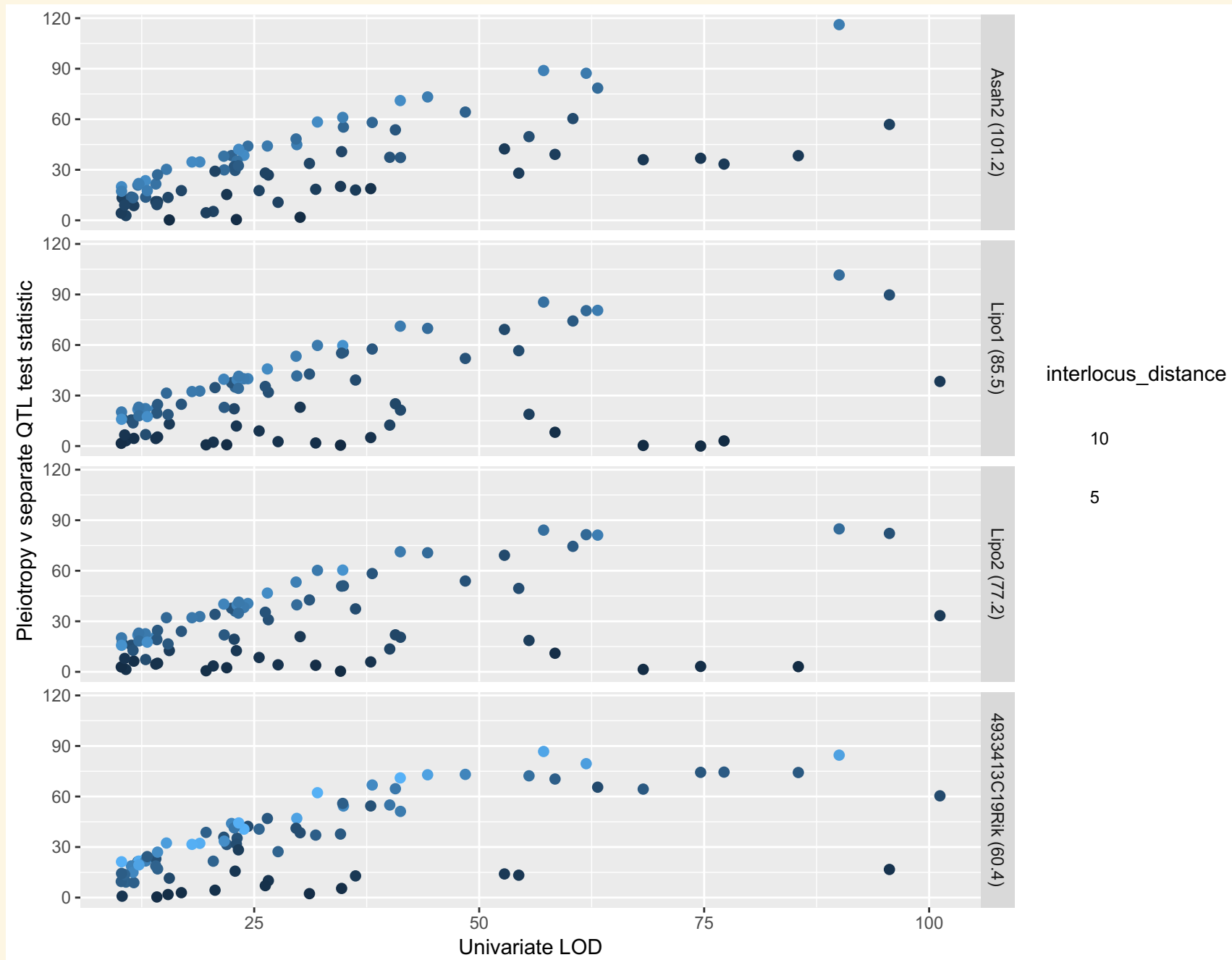
Power study: Conclusions

- $\uparrow$ Interlocus distance $\uparrow$ Pleiotropy test statistics

- $\uparrow$ Univariate LOD $\uparrow$ Pleiotropy test statistics

qtl2pleio R package

qtl2pleio R package

- Functions for d-variate, d-QTL scan & profile LOD plots

- Uses C++ for matrix calculations (via Rcpp and RcppEigen)

- Uses `gemma2` R implementation of GEMMA EM algorithm for multivariate random effects

- Unit tests, vignettes, and version control

Thank you!

References

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

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

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: *Mammalian genome* 25.5-6, pp. 211-222.